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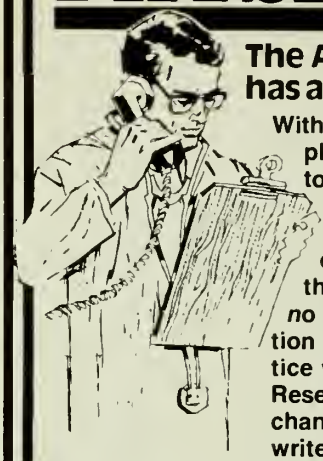

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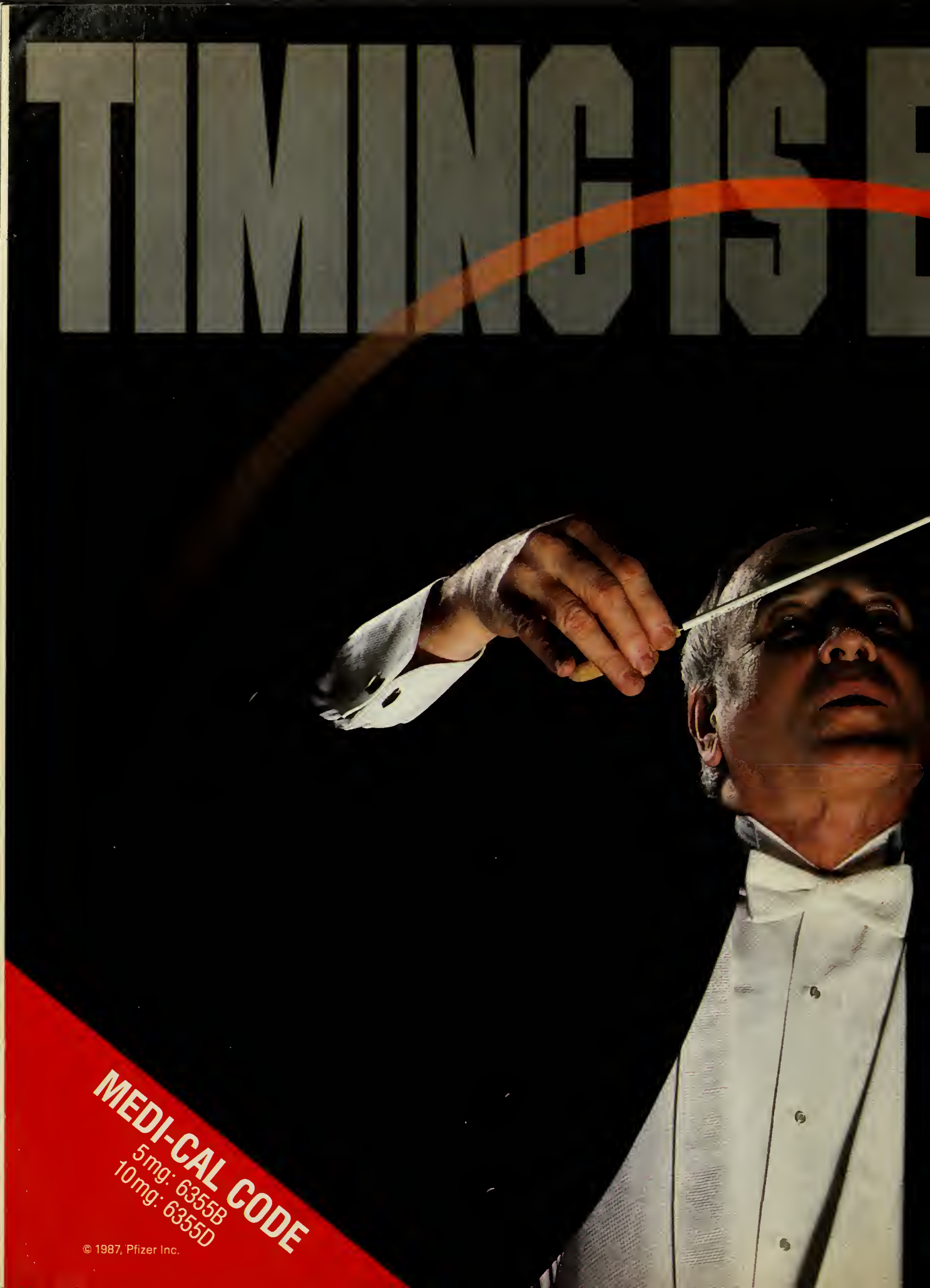

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UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

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Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia Proper patient selection, dosage and instructions are important to avoid hypoglycemia Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery It may then be necessary to discontinue GLUCOTROL and administer insulin

Laboratory Tests: Blood and urine glucose should be monitored periodically Measurement of glycosylated hemoglobin may be useful

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members Primary and secondary failure should also be explained

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol However, caution must be exercised in extrapolating these findings to a clinical situation Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity Bacterial and *in vivo* mutagenicity tests were uniformly negative Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility

Pregnancy: Pregnancy Category C GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg) This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL In studies in rats and rabbits no teratogenic effects were found There are no adequate and well-controlled studies in pregnant women GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery This has been reported more frequently with the use of agents with prolonged half-lives GLUCOTROL should be discontinued at least one month before the expected delivery date

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low Of 702 patients, 11 8% reported adverse reactions and in only 1 5% was GLUCOTROL discontinued

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100 They appear to be dose-related and may disappear on division or reduction of dosage Cholestatic jaundice may occur rarely with sulfonylureas GLUCOTROL should be discontinued if this occurs

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL They are usually transient and seldom require discontinuance of therapy

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL, in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia

Initial Dose: The recommended starting dose is 5 mg before breakfast Geriatric patients or those with liver disease may be started on 2 5 mg Dosage adjustments should ordinarily be in increments of 2 5-5 mg, as determined by blood glucose response At least several days should elapse between titration steps

Maximum Dose: The maximum recommended total daily dose is 40 mg

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing Total daily doses above 15 mg should ordinarily be divided

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100, 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

CAUTION: Federal law prohibits dispensing without prescription

More detailed professional information available on request.

ROERIG Pfizer A division of Pfizer Pharmaceuticals New York, New York 10017

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ABDOMINAL ULTRASOUND—Carol A. Mittelstaedt, MD, Associate Professor, Radiology and Obstetrics and Gynecology, University of North Carolina at Chapel Hill. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 711 pages, $149.

BODY FLUID HOMEOSTASIS—Volume 16 in Contemporary Issues in Nephrology—Edited by Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School, and Director, Renal Division and Laboratory of Kidney and Electrolyte Physiology, Brigham and Women's Hospital, Boston, and Jay H. Stein, MD, Professor and Chairman, Department of Medicine, University of Texas Health Science Center at San Antonio. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 438 pages, $62.

CLINICAL ELECTROCARDIOGRAPHY—A Primary Care Approach—Ken Grauer, MD, Associate Professor, and R. Whitney Curry, Jr, MD, Associate Professor and Associate Chairman, Department of Community Health and Family Medicine, University of Florida College of Medicine, Gainesville. Medical Economics Books, Oradell, NJ 07649, 1987. 539 pages, $24.95 (paperback).

COMPUTED TOMOGRAPHY OF THE MUSCULOSKELETAL SYSTEM—Volume 8 in Contemporary Issues in Computed Tomography—Edited by William W. Scott, Jr, MD, Associate Professor, The Russell H. Morgan Department of Radiology and Radiological Science, Director of Musculoskeletal Imaging and Director of Medical Student Education in Radiology; Donna Magid, MD, Assistant Professor, The Russell H. Morgan Department of Radiology and Radiological Science, Division of Musculoskeletal Imaging, and Assistant Professor, Orthopaedic Surgery, and Elliot K. Fishman, MD, Associate Professor, The Russell H. Morgan Department of Radiology and Radiological Science, and Director, Division of Computed Body Tomography, The Johns Hopkins Medical Institutions, Baltimore. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 260 pages, $39.

DEAR DOCTOR—A PERSONAL LETTER TO A PHYSICIAN—Charles E. Odegaard, President Emeritus, University of Washington, Seattle. The Henry J. Kaiser Family Foundation, 525 Middlefield Rd, Suite 200, Menlo Park, CA 94025. 172 pages (paperback); single copies available at no charge, subsequent copies $3 each.

DUBOIS' LUPUS ERYTHEMATOSUS—3rd Ed—Edited by Daniel J. Wallace, MD, Assistant Clinical Professor of Medicine, University of California, Los Angeles; Attending Physician, Cedars-Sinai Medical Center, Los Angeles, and Chief Rheumatology Consultant, City of Hope, Duarte, California, and Edmund L. Dubois, MD (Deceased), Clinical Professor of Medicine, University of Southern California School of Medicine, and Director, Collagen Disease Clinic, Los Angeles County-USC Medical Center, Los Angeles. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106-4198, 1987. 749 pages, $98.50.

THE GOOD NEWS ABOUT DEPRESSION—CURES AND TREATMENTS IN THE NEW AGE OF PSYCHIATRY—Mark S. Gold, MD, Director of Research, Fair Oaks Hospital, Summit, NJ, and Founder of the National Cocaine Hotline and Psychiatric Diagnostic Laboratories of America. Villard Books, New York, NY 10022. 311 pages, $18.95.

GROWTH ABNORMALITIES—Volume 4 in Contemporary Issues in Endocrinology and Metabolism—Edited by Raymond L. Hintz, MD, Professor of Pediatrics, and Ron G. Rosenfeld, MD, Associate Professor of Pediatrics, Division of Pediatric Endocrinology, Department of Pediatrics, Stanford University School of Medicine, Stanford, California. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 274 pages, $42.

INFECTION CONTROL IN INTENSIVE CARE—Volume 12 in Clinics in Critical Care Medicine—Edited by Bruce F. Farber, MD, Assistant Professor of Medicine, Cornell University Medical College, New York; Chairman, Infection Control Committee, and Attending Physician, Division of Infectious Diseases and Immunology, Department of Medicine, North Shore University Hospital, Manhasset, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 203 pages, $28.

INTERVENTIONAL ULTRASOUND—Volume 21 in Clinics in Diagnostic Ultrasound—Edited by Eric vanSonnenberg, MD, Associate Professor of Radiology and of Medicine, Department of Radiology, University of California, San Diego, School of Medicine, La Jolla, and Chief, Gastrointestinal and Interventional Radiology, UCSD Medical Center, San Diego. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 234 pages, $32.

MANUAL OF CHILD NEUROLOGY—Owen B. Evans, MD, Director, Pediatric Neurology, and Associate Professor of Pediatrics and Neurology, University of Mississippi School of Medicine, Jackson. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 425 pages, $39 (paperback).

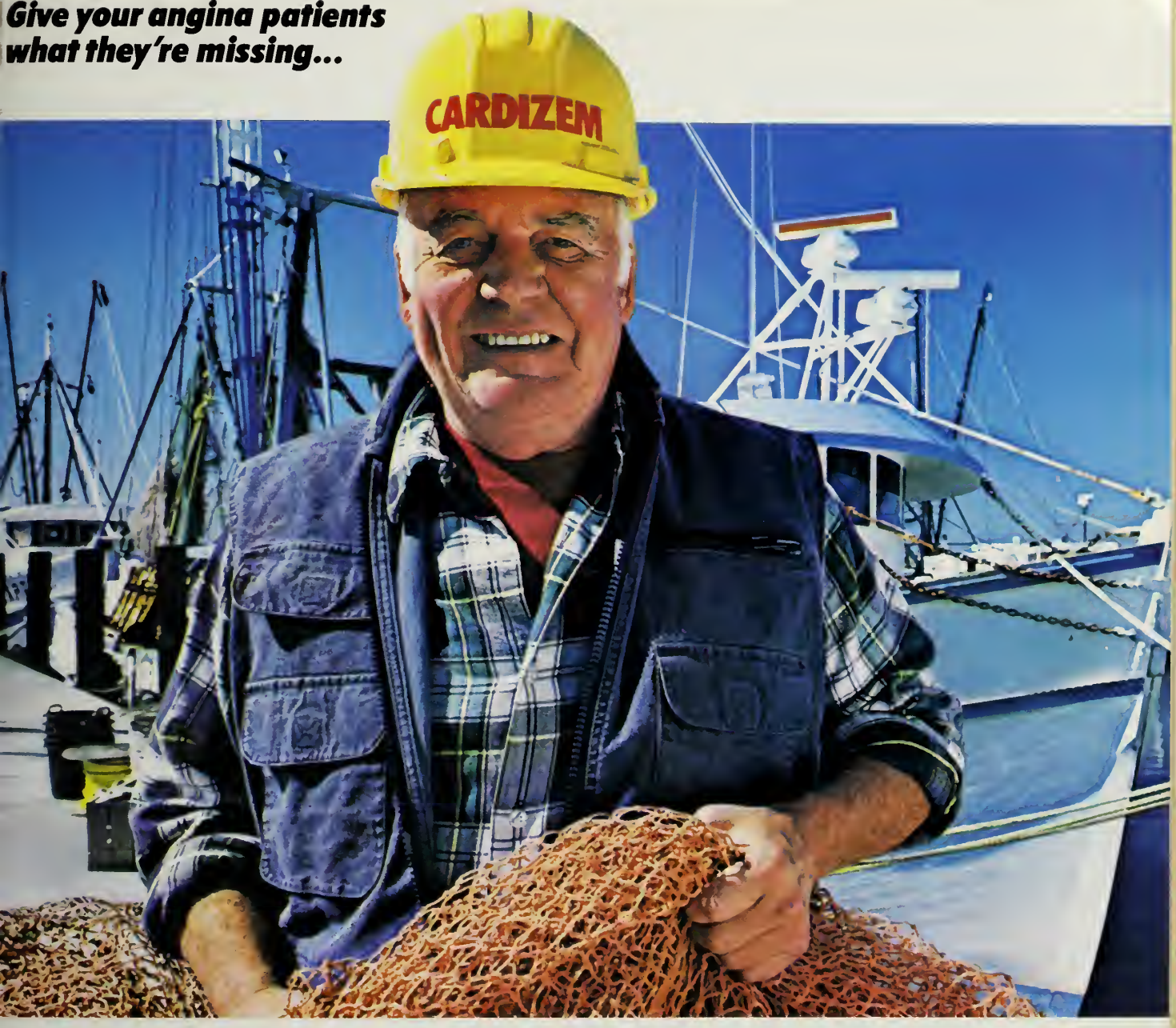
MANUAL OF CORNEAL SURGERY—Edited by William E. Bruner, MD, Assistant Professor of Ophthalmology, Case Western Reserve University School of Medicine, University Suburban Health Center, Cleveland; Walter J. Stark, MD, Professor of Ophthalmology, and A. Edward Maumenee, MD, Professor of Ophthalmology, Wilmer Ophthalmological Institute, The Johns Hopkins University School of Medicine, Baltimore. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 133 pages, $32 (paperback).

MANUAL OF PEDIATRIC EMERGENCIES—Edited by Joseph R. Zanga, MD, Associate Professor of Pediatrics and Director, Section of Ambulatory and Emergency Care, Children's Medical Center, Medical College of Virginia, Virginia Commonwealth University, Richmond. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 484 pages, $38.50 (paperback).

ORGANIZATIONAL STRUCTURE, PROBLEM SOLVING, AND EFFECTIVENESS—A COMPARATIVE STUDY OF HOSPITAL EMERGENCY SERVICES—Basil S. Georgopoulos, Research Scientist, Institute for Social Research, and Professor of Psychology, University of Michigan, Ann Arbor. Jossey-Bass Inc, Publishers, 433 California St, San Francisco, CA 94104, 1986. 381 pages, $32.95.

RENAL DISEASE—A CONCEPTUAL APPROACH—E. Kinsey M. Smith, MD(Lond), FRCP, FRCP(C), Professor, Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 143 pages, $12.50 (paperback).

Give your angina patients what they're missing...



CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- ***Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate***
- ***Proven efficacy when used alone in angina[1]***
- ***Compatible with other antianginals[2,3*]***
- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

90 mg NEW 120 mg GREATER DOSAGE FLEXIBILITY

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.

CARDIZEM® diltiazem HCl/Marion

FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

60 mg tid or qid

Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 7/86

See complete Professional Use Information before prescribing.

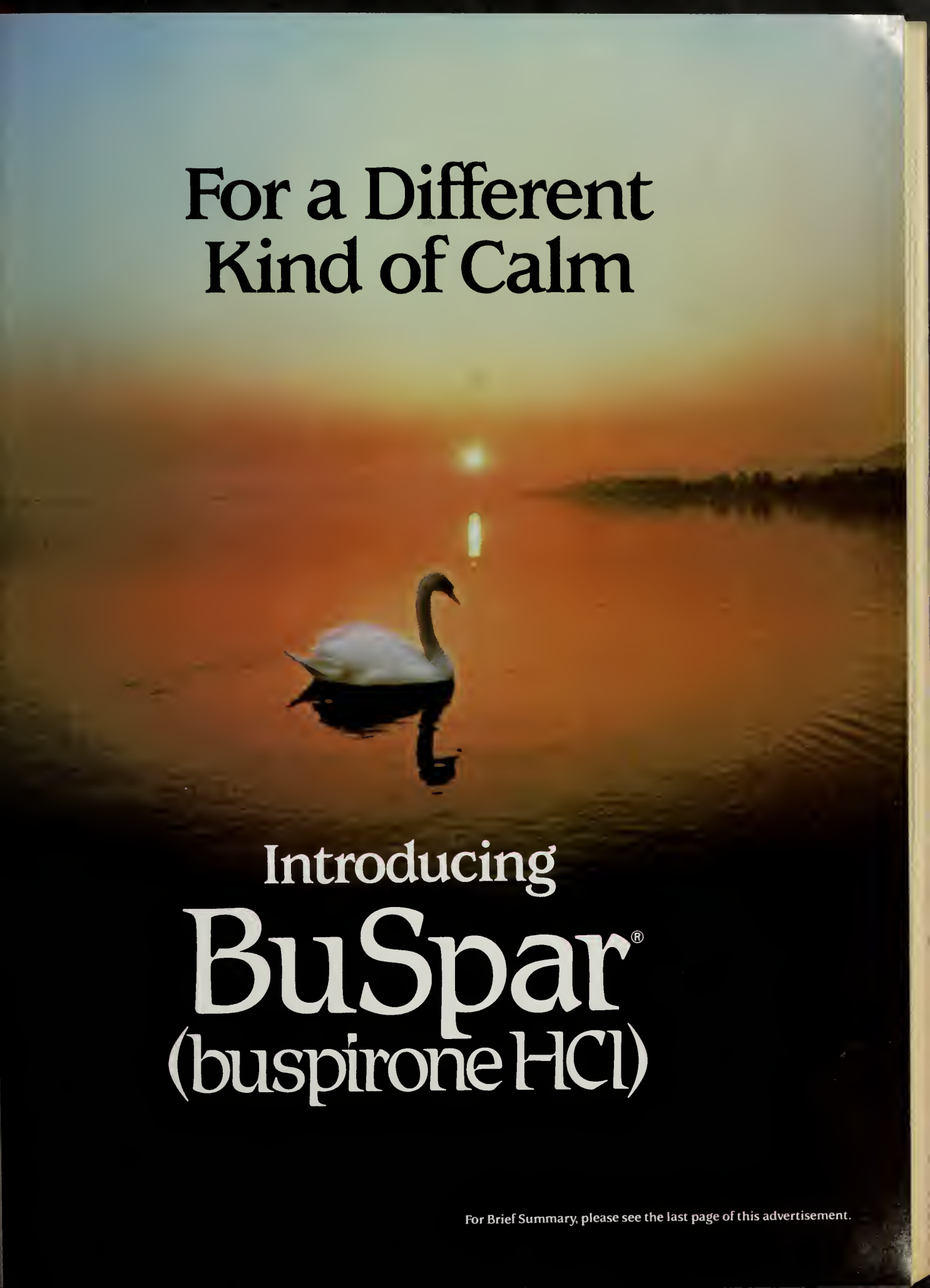
References: 1. Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347. **2.** Shapira W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159. **3.** Johnston DL, Lesaway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985,55:680-687. **4.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **5.** Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982,50(Sept):94-116.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

0246M6

For a Different Kind of Calm



Introducing BuSpar® (buspirone HCl)

For Brief Summary, please see the last page of this advertisement.

Mead Johnson
Pharmaceuticals
Introduces

BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

A different kind of calm

BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.[1,2,3]

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.[4,5]

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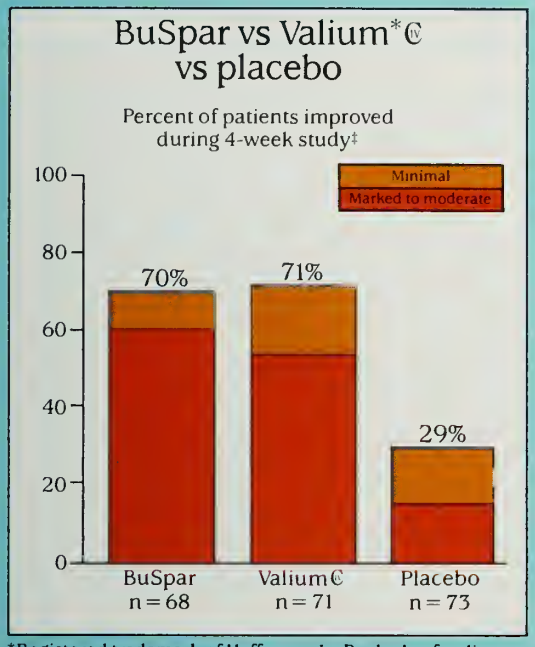
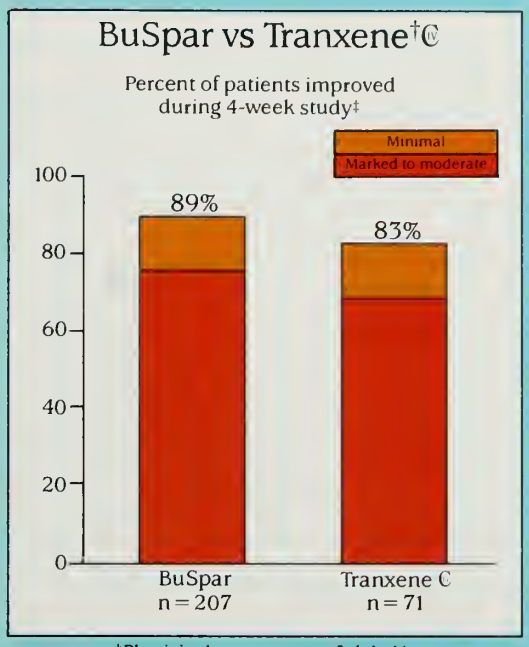
Proven anxiolytic effectiveness over a 4-week course of therapy[6,7]





*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.
‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,* and cardiovascular and gastrointestinal complaints.

*BuSpar is not indicated for the treatment of primary depressive disorder.

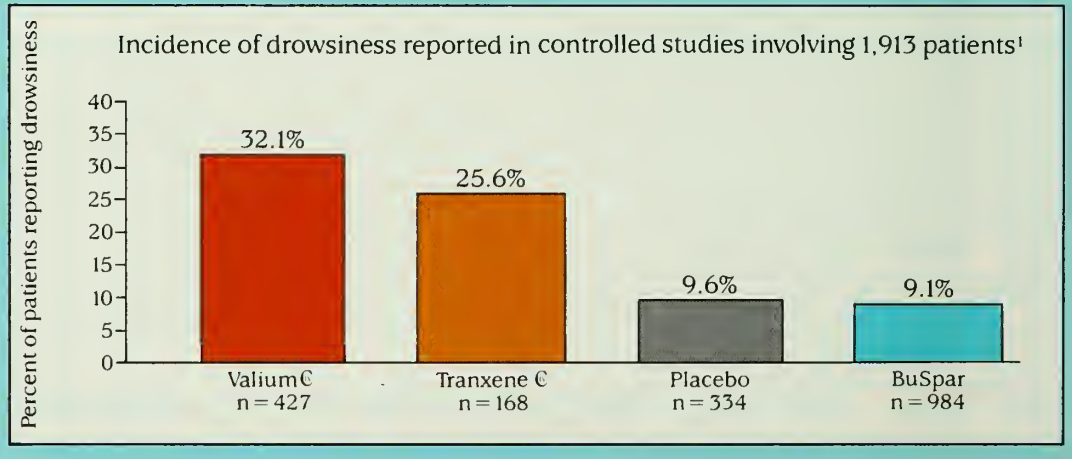
For Brief Summary, please see the last page of this advertisement.

BuSpar®
Tablets
5 mg and 10 mg
(buspirone HCl)

Anxiolytic efficacy without CNS-depressant activity

Incidence of drowsiness no greater than placebo

Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.[1]



No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.[2]

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.*[3]

No apparent abuse liability

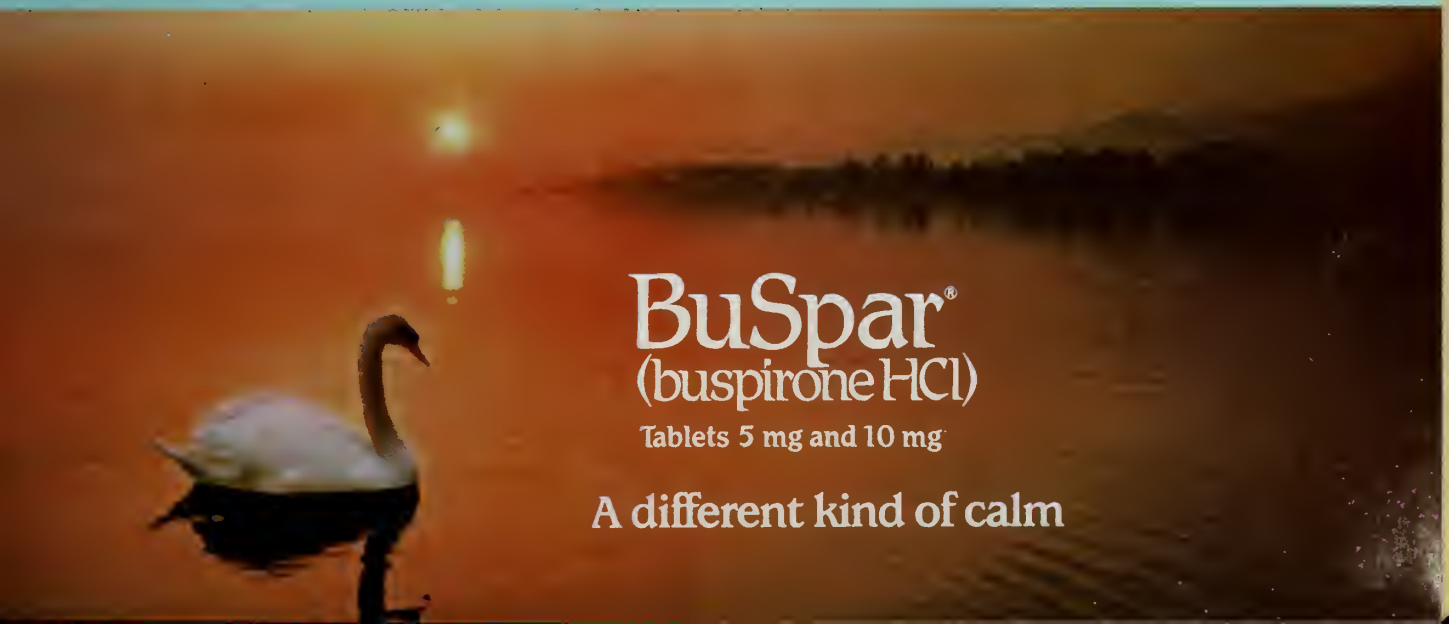
Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.[4,8]

Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

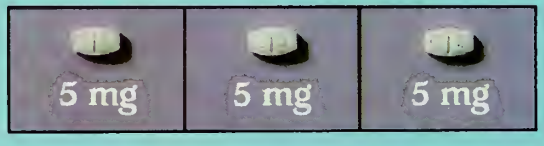
Subtle onset of effect

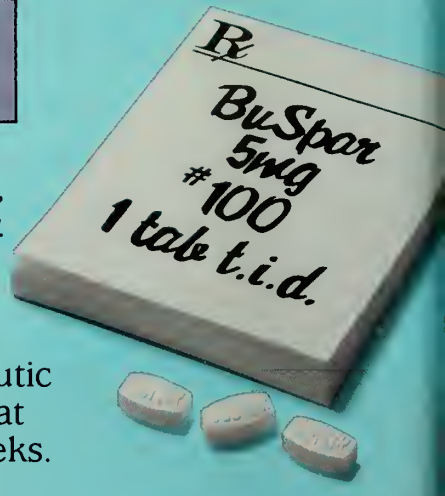
BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1





Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is <u>not</u> a controlled substance.

Patient selection

BuSpar will not block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

If you elect to switch a patient from a benzodiazepine to BuSpar:

1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

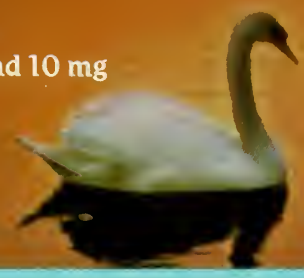
BuSpar...the first choice in anxiolytic therapy when:

- ☑ Treatment requires regular dosing for more than a few days
- ☑ Patient functioning is key to safe and successful treatment
- ☑ The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.

BuSpar® (buspirone HCl)

Tablets
5 mg and 10 mg



For a different kind of calm

CONTRAINDICATIONS:
Hypersensitivity to buspirone.

WARNINGS:
The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:
Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers:
Administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly:
No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%. **CNS:** dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** blurred vision 2%. **Gastrointestinal:** nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** musculoskeletal aches/pains 1%. **Neurological:** numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. **Skin:** skin rash 1%. **Miscellaneous:** headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular:** Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. **Central Nervous System:** Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. **EENT:** Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. **Endocrine:** Rare were galactorrhea and thyroid abnormality. **Gastrointestinal:** Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. **Genitourinary:** Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. **Musculoskeletal:** Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. **Neurological:** Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. **Respiratory:** Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. **Sexual Function:** Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence. **Skin:** Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails. **Clinical Laboratory:** Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia. **Miscellaneous:** Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

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Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)" and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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The Western Journal of Medicine

VOLUME 147 • NUMBER 1 • JULY 1987

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(nadolol tablets)

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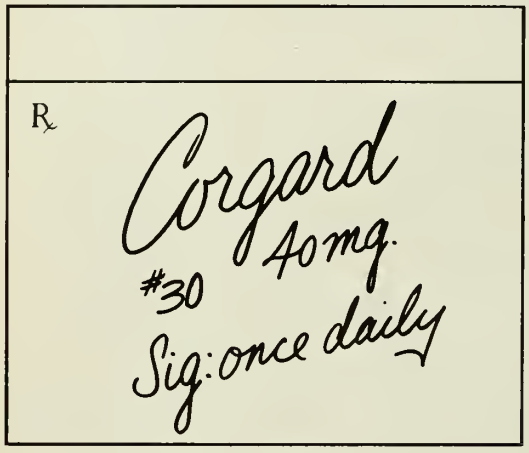

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DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect, monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

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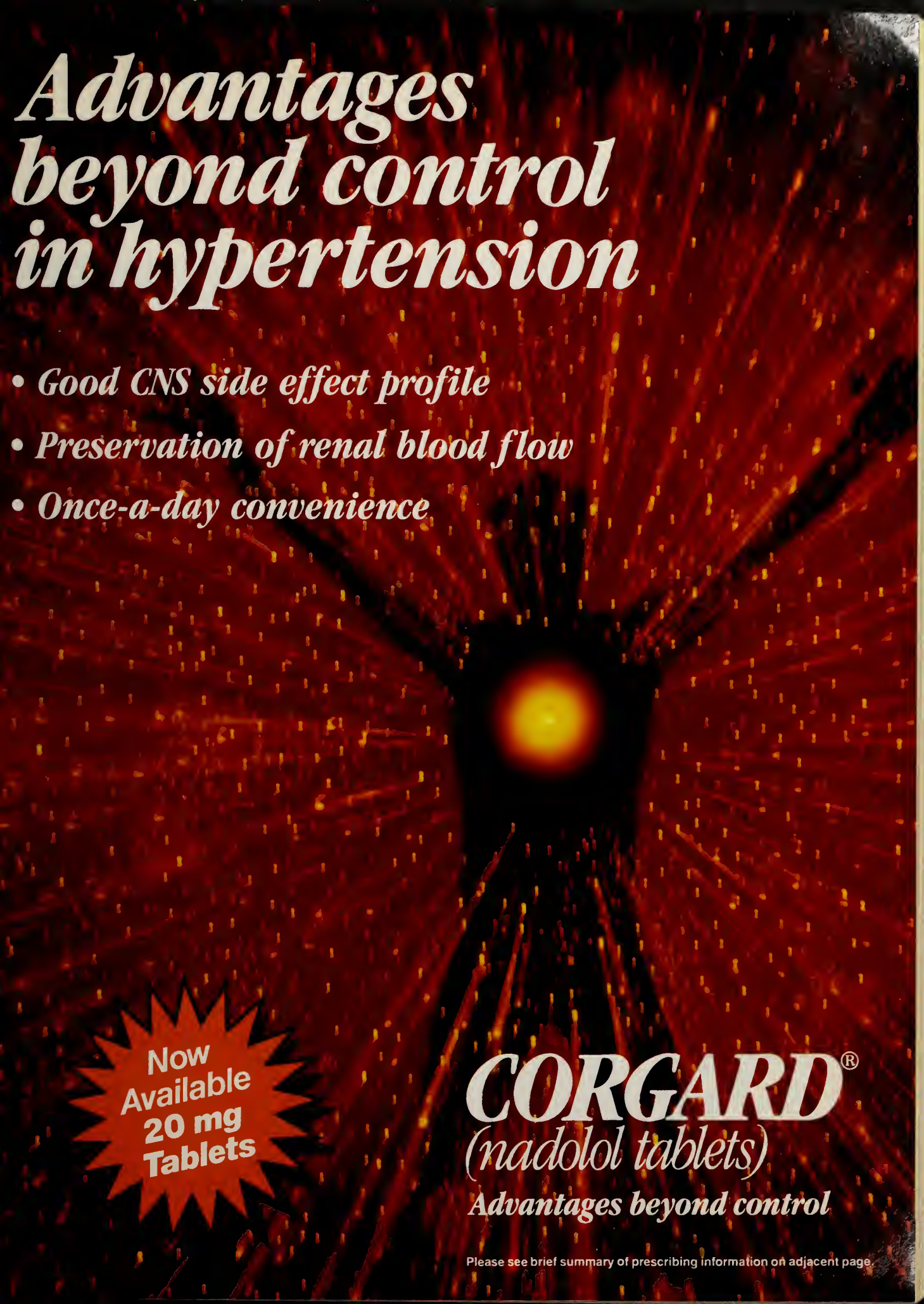
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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients, this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined, (2) to contact the physician if any difficulty in breathing occurs, (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations, congestive heart failure, peripheral edema, and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 24-26—**Coconino County Medical Society Summer Medical Seminar and Day of Surgery.** DuBois Conference Center at Northern Arizona University, Flagstaff. Fri-Sun. Contact: Coconino County Medical Society, (602) 774-7694.

August 6-8—**Current Management and Future Trends in Cognitive Impairment and Motor Dysfunction in Parkinson's.** Hassayampa Inn, Prescott. Thurs-Sat. Contact: Ann McKinley, (602) 445-2700.

November 5-7—**Gynecologic Surgery: Principles, Techniques and Management of Complications.** Hyatt Regency, Scottsdale. Thurs-Sat. Contact: Robin Murray, ACOG, (202) 638-5577, ext 343.

November 16-17—**Update on Management of Spina Bifida.** La Posada Resort, Scottsdale. Mon-Tues. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800)-BARROW-1.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

August 23-28—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Royal Waikoloa Hotel, The Big Island, Hawaii. Sun-Fri. 20 hrs. $375. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 12-13—**Case Conference on Clinical Anesthesiology.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $160. Contact: California Society of Anesthesiologists, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Westin Maui, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiology, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

September 12—**Advances in Lung Cancer.** UCI at Long Beach. Sat. Contact: UCI.

October 19-21—**11th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 21 hrs. $350. Contact: Nomi Feldman, Scripps Memorial Hospital, 3770 Tansy, San Diego 92121. (619) 453-6222.

December 9—**23rd Northern California Cancer Conference.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th and The Esplanade, Chico 95926. (916) 891-7300.

December 12—**Bronchology Laser Cancer Symposium.** UCI at Long Beach. Sat. Contact: UCI.

CARDIOLOGY

July 17-18—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 26-August 8—**13th Ten Day Seminar on Epidemiology and Prevention of Cardiovascular Disease.** American Heart Association at Lake Tahoe, Nevada. Sun-Sat. Contact: AHA, 7320 Greenville Ave, Dallas, TX 75231.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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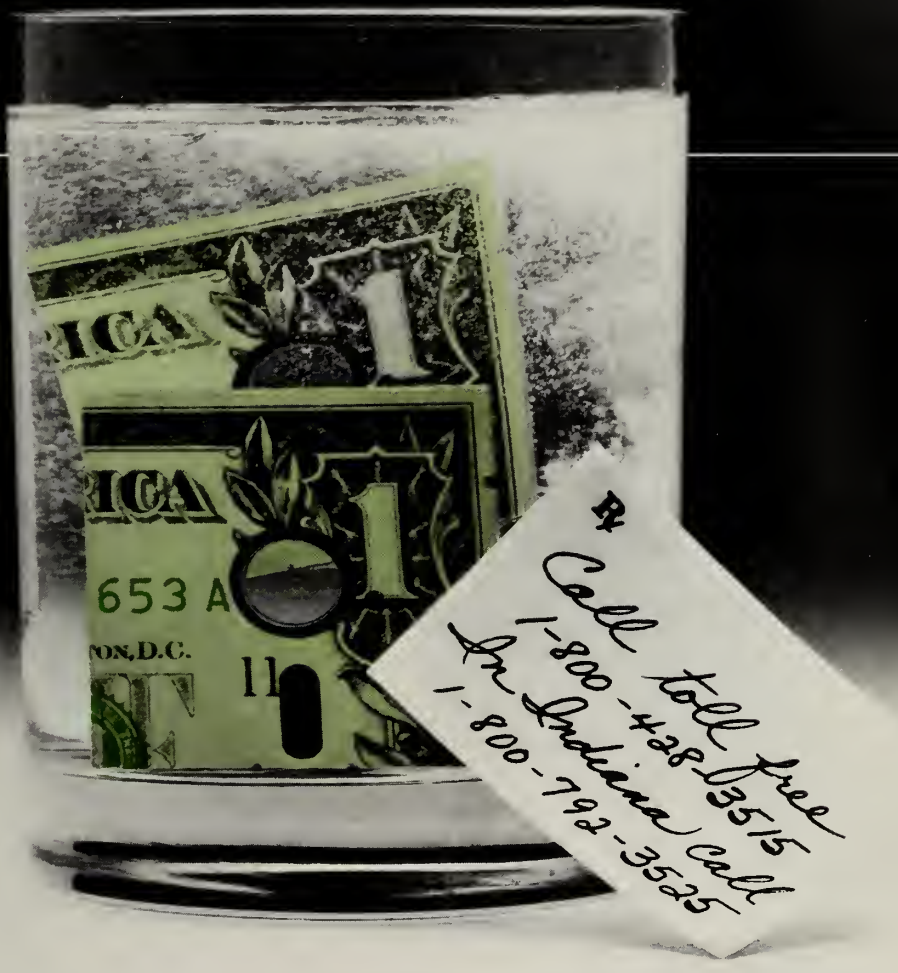

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Physicians Practice Management
1810 S. Lynhurst, Suite Q, Indianapolis, Indiana 46241
Software for the M.D.

The portrait of anxiety

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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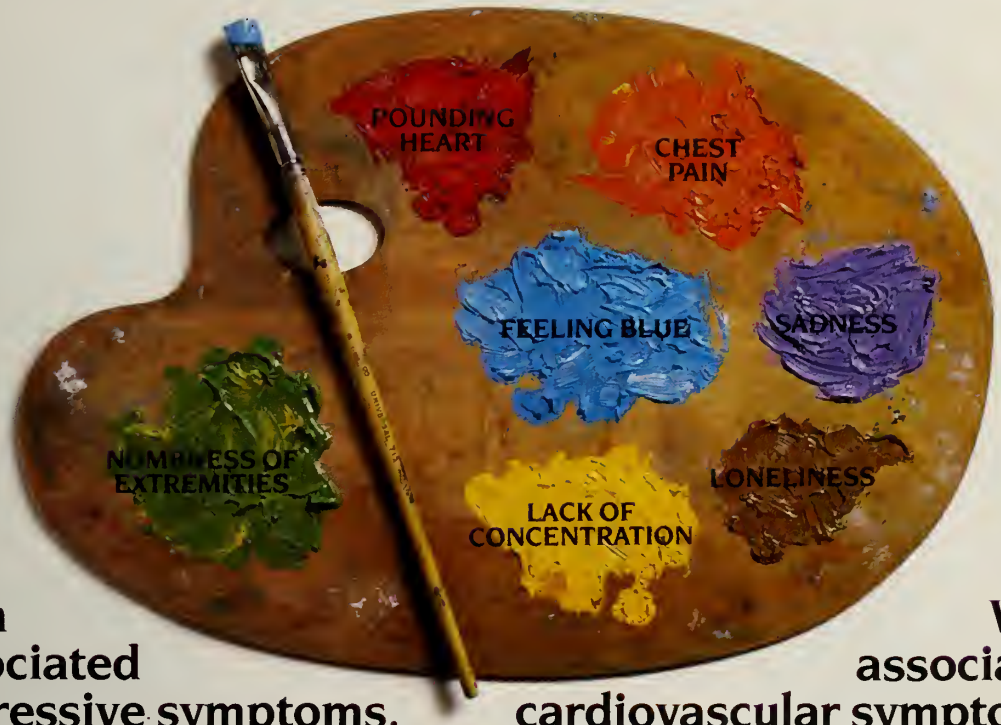
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax® alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

Upjohn THE UPJOHN COMPANY J-7384
Kalamazoo, Michigan 49001 USA February 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 22)

July 31-August 1—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Harvey's Hotel, Lake Tahoe, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 2-7—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

August 7-8—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

September 11-13—**Advanced Cardiac Life Support.** CPR Seminars at Incline Village, Lake Tahoe, Nevada. Fri-Sun. $170. Contact: CPR Seminar, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

September 12—**57th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Association, San Francisco at Cathedral Hill Hotel, San Francisco. Sat. 9 hrs. $100. Contact: AHA, 42 Powell St, San Francisco 94102. (415) 433-2273

September 17-18—**Optimal Coronary Revascularization.** Santa Barbara Medical Foundation Clinic, Sansum Medical Clinic and Santa Barbara Cottage Hospital at Red Lion Resort Hotel, Santa Barbara. Thurs-Fri. 14 hrs. $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sun. 13 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

September 25-27—**International Workshop on Future Directions in Interventional Cardiology.** American College of Cardiology at Red Lion Resort, Santa Barbara. Fri-Sun. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (800) 253-4636, ext 226, or (301) 897-5400.

October 15-17—**11th Annual Seminar: Cardiology Update 1987.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

October 15-17—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 30-31—**Coronary Heart Disease.** Medical Education Resources at Las Vegas Hilton Hotel, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 13-14—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hilton Hotel, San Francisco. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 14—**16th Annual Cardiology Symposium.** Fresno Community Hospital at Center Plaza Hotel, Fresno. Sat. Contact: Joann Ellis, Fresno Community Hospital, PO Box 1232, Fresno 93715. (209) 442-3936.

December 4-5—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

DERMATOLOGY

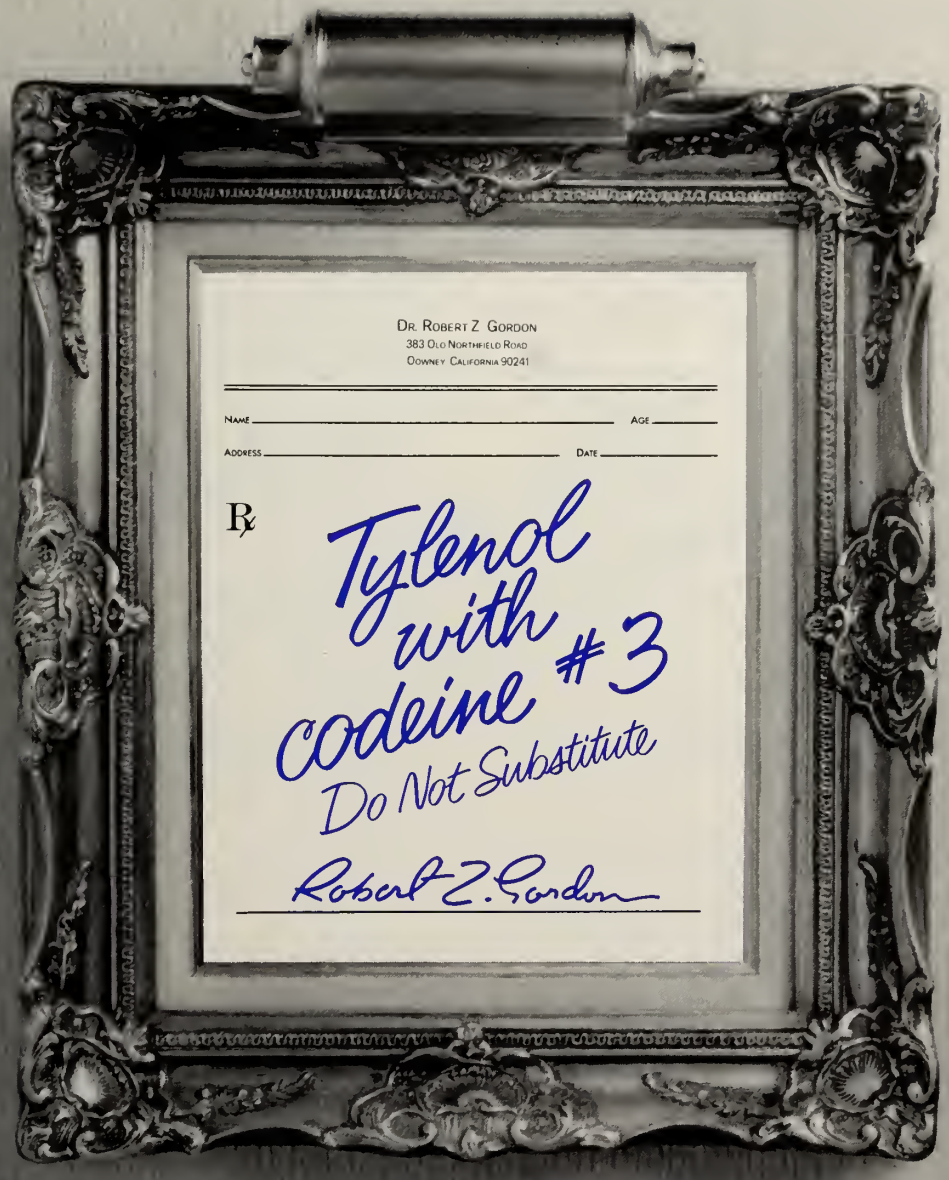
July 15-19—**American Academy of Dermatology Summer Session.** At Anaheim. Wed-Sun. 29 hrs. Contact: American Academy of Dermatology, 1567 Maple Ave, Box 3116, Evanston, IL 60204-3116.

August 13-15—**Problems of the Aging Skin.** STAN at Hyatt Rickeys Hotel, Palo Alto. Thurs-Sat. Contact: STAN.

August 14-15—**Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, Director, 412 W Carroll, Glendora 91740. (818) 963-7684.

October 24-25—**16th Annual Mycology Review.** STAN at STAN. Sat-Sun. Contact: STAN.

(Continued on Page 28)



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*Warning: May be habit forming.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 26)

EMERGENCY MEDICINE

July 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center. San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

July 24-26—**Sports Medicine Updates.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

July 31-August 2—**Topics in Emergency Medicine.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

August 12-16—**Wilderness Medicine: 1987.** Siskiyou General Hospital at Northstar, Tahoe Resort. Wed-Sun. 20 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (916) 842-6848.

August 14-16—**Update on Trauma.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

August 17-21—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Lab.** UCSD at UCSD. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

August 21-23—**Sports Medicine Updates.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 31-September 4—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

September 5-7—**Wilderness Medicine.** J. Bear Co at Klamath River (whitewater rafting). Sat-Mon. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

September 11-13—**Advanced Cardiac Life Support.** CPR Seminars at Incline Village, Lake Tahoe, Nevada. Fri-Sun. $170. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

September 13-20—**Diving and Marine Medicine.** J. Bear Co at Lahaina, Maui, Hawaii. One week. 10 hrs. $850. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550.

INTERNAL MEDICINE

July 18-20—**8th Annual Symposium on Laboratory and Clinical Aspects of Microbiological Diagnosis.** UCLA at Hyatt Regency Hotel, Monterey. Sat-Mon. 13 hrs. $175. Contact: UCLA.

August 23-28—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $395. Contact: UCD.

October 10—**Clinical Update on Thromboembolic Disease and Anticoagulation.** UCD at Hilton Hotel, Sacramento. Sat. Contact: UCD.

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

November 11—**Gastroenterology.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

OB/GYN

July 16-18—**Developmental Interventions in Neonatal Care.** American Academy of Pediatrics at San Francisco. Thurs-Sat. 17 hrs. Contact: Contemporary Forums, 530 La Gonda Way, Ste E, Danville 94526. (415) 820-2800.

September 19-22—**The Fetus and Newborn.** Contemporary Forums at San Diego. Sat-Tues. Contact: Contemporary Forums, 530 La Gonda Way, Ste E, Danville 94526. (415) 820-2800.

October 16-18—**Advanced Fetal Heart Rate Monitoring.** UCI at Embassy Suites Hotel, Napa Valley. Fri-Sun. Contact: UCI.

December 4-5—**Environmental Exposure and Fetal Development (March of Dimes).** UCD at Sacramento Inn. Fri-Sat. Contact: UCD.

OPHTHALMOLOGY

August 1-8—**Ophthalmology.** USC at Mauna Kea, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 30-Sept 2—**Under Pressure: Glaucoma 1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. Contact: UCD.

December 10-11—**Ophthalmic Plastic and Reconstructive Surgery: Past, Present, and Future—A Tribute to Crowell Beard, MD.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

PATHOLOGY

August 22-29—**7th Annual Symposium on Fine Needle Aspiration.** California Society of Pathologists and UCSF at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. One week. 24.5 hrs. Contact: UCSF.

October 3—**Fine Needle Aspiration Tutorial.** UCSF at UCSF. Sat. 7 hrs. $475. Contact: UCSF.

PEDIATRICS

July 24-25—**Debates and Updates in Pediatric Emergencies.** UCSF at Hyatt on Union Square, San Francisco. Fri-Sat. 14 hrs. $235. Contact: UCSF.

July 31-August 1—**Pediatric Emergencies.** UCSF. Fri-Sat. Contact: UCSF.

September 12-13—**44th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sheraton Universal Hotel, Los Angeles. Sat-Sun. Contact: Los Angeles Pediatric Society, PO Box 9022, Inglewood 90305. (213) 757-1198.

October 10-17—**11th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea Beach, Hawaii. One week. Contact: UCI.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 16-18—**Current Advances in Pediatrics.** American Academy of Pediatrics and UCI at Disneyland Hotel, Anaheim. Fri-Sun. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

October 23-25—**Current Concepts in Pediatric Gastroenterology.** Children's Hospital, Oakland at Doubletree Hotel, Monerey. Fri-Sun. Contact: Kim Leadon, CME Office, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

November 20-23—**9th Annual Las Vegas Seminars—Pediatric Update.** Los Angeles Pediatric Society at Caesar's Palace. Fri-Mon. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

October 17-18—**Dynamics of Human Development—Implications for Treatment.** Continuing Education Seminars at Los Angeles. Sat-Sun. 11.5 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave, Los Angeles 90024. (213) 475-8300.

November 6-8—**33rd Annual: Group Therapy Symposium.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sun. Contact: UCSF.

(Continued on Page 30)

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Issued: July 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 28)

RADIOLOGY

August 3-7—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 27.5 hrs. $495. Contact: UCSF.

August 3-7—**Modern Radiology Practice.** UCSD at Red Lion Ocean Resort, Santa Barbara. Mon-Fri. 30 hrs. $250-425. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 8-9—**Magnetic Resonance Imaging Update and New Techniques: A Mini-Symposium.** Hoag Memorial Presbyterian Hospital at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 12 hrs. $175. Contact: Dawne Ryals, PO Box 920113. (404) 641-9773.

August 13-15—**Advanced Ultrasound.** American College of Obstetricians and Gynecologists at Silverado Inn, Napa. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave SW, Washington, DC 20024-2588. (202) 638-5577.

August 22-29—**Radiology.** USC at Maui Marriott Hotel, Maui, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 26-28—**Interventional Radiology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. Contact: UCSF.

August 27-30—**3rd Annual Physics and Biology of Radiology.** UCSD at San Diego Town and Country Hotel. Thurs-Sun. 26.5 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 28-30—**3rd Annual Sonographers' Update and Review.** UCSD at Bahia Resort Hotel, San Diego. Fri-Sun. 16 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 29-30—**Advances in Imaging Technology.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

September 10-12—**Contemporary Diagnostic Imaging: CT, Interventional, MRI, US.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

September 10-12—**Advances in Sectional Imaging.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 14 hrs. $375. Contact: UCSD.

September 10-13—**Physics of Diagnostic Radiology.** UCD at UCD. Thurs-Sun. 25 hrs. Contact: UCD.

September 17-19—**Ultrasound Workshop.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

October 17-18—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. Contact: UCSF.

October 19-23—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. $495. Contact: UCSF.

October 19-23—**12th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 28 hrs. $425. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

SPORTS MEDICINE

July 24-26—**Sports Medicine Updates.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

July 27-31—**Sports Medicine Update—1987.** UCSD at San Diego Princess Hotel, Vacation Village. Mon-Fri. 29.5 hrs. $325. Contact: UCSD.

August 21-23—**Sports Medicine Updates.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

SURGERY

September 14-17—**Cochlear Implant Training—1987.** House Ear Institute, Los Angeles. Mon-Thurs. 24 hrs. $250. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

September 26-27—**Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at Los Angeles. Sat-Sun. 12 hrs. Contact: Terri Harrington, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 4-10—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 5—**Wrist Arthroscopy.** American Society for Surgery of the Hand at San Diego. Mon. Contact: Paula Scheid, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 17-18—**Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at San Francisco. Sat-Sun. 12 hrs. Contact: Terri Harrington, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-24—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 21—**Primary Care Course.** American Society for Surgery of the Hand at Los Angeles. Sat. 7 hrs. Contact: Anne Turner, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 6-12—**Temporal Bone Surgical Dissection—1987.** House Ear Institute at House Ear Institute, Los Angeles. Sun-Sat. 62 hours. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

July 24-30—**International CME for Physicians.** Boston University at Pebble Beach. Fri-Thurs. 20 hrs. $350. Contact: Boston University, 80 E Concord St, Boston, MA 02118.

July 28-August 8—**Medical Ethics and Humanities.** UCSF at San Francisco. Tues-Sat. 59 hrs. $1200. Contact: UCSF.

August 6-9—**American Association of Sex Educators, Counselors, and Therapists Annual: Skills Update II.** At Las Vegas, Nevada. Thurs-Sun. 18 hrs. $150. Contact: William Stull, AASECT, 2333 N 3rd St, Phoenix, AZ 85004. (602) 252-2706.

August 16-26—**30th Anniversary Postgraduate Refresher Course—Program I.** USC at Sheraton Waikiki Hotel, Honolulu and the Marriott Hotel, Maui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1919, outside California, (800) 421-6729.

August 20-21—**6th Annual: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Wed-Thurs. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hosptial, 150 Pioneer Lane, Bishop 93514. (619) 873-5811.

August 23-September 2—**30th Anniversary Postgraduate Refresher Course—Program II.** USC at Marriott Hotel, Maui and the Waiohai Hotel, Kaui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1929, outside California, (800) 421-6729.

August 30—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Newporter Resort, Newport Beach. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 9-11—**Primary Care Medicine: Principles and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 20 hrs. $365. Contact: UCSF.

September 13—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 14-18—**STD Clinician Training Course—Intensive.** Long Beach Health Dept. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

September 16—**Common Office Pediatric and Dermatology Cases.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

(Continued on Page 31)

CONTINUING MEDICAL EDUCATION

(Continued from Page 30)

September 20—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-22—**7th Annual Bristol-Myers Symposium on Nutrition Research: Nutrition and the Origins of Disease.** UCD at Fairmont Hotel, San Francisco. Mon-Tues. Contact: UCD.

October 14—**17th Annual Respiratory Medicine.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

October 16-18—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $365. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-22—**Annual Family Practice Update.** Mon-Thurs. LLU at LLU. Contact: LLU.

October 19-30—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI at Long Beach. Mon-Fri. Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

October 26-November 1—**Traumatic Brain Injury.** UCD at Red Lion Motor Inn, Sacramento. Mon-Sun. Contact: UCD.

November 12-14—**2nd Annual: Progress in Impotence—Workshops/Seminars.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. 13 hrs. $295. Contact: Edith Bookstein/UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 18—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service, (117) VAMC, 16111 Plummer St, Sepulveda 91343. (818) 891-2473.

November 22—**Controversy in Modern Medicine—1987.** Granada Hills Community Hospital and UCLA at Sheraton Universal Hotel, N Hollywood. Sun. 7 hrs. $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021.

December 7-18—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

IDAHO

July 27-August 2—**Idaho Medical Association Annual Meeting.** Coeur d'Alene. One week. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 1-8—**Forefronts in Pediatrics.** Sun Valley. One week. Sponsored by the University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions. 24 hrs. Contact: Kathy Rairigh, EPIC EXPEDITIONS, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

August 13-15—**Sun Valley Emergency Medical Conference.** Convention Center, Sun Valley. Thurs-Sat. Contact: Idaho EMS System, 450 W State St, Boise 83720. (208) 334-5994.

(Continued on Page 111)

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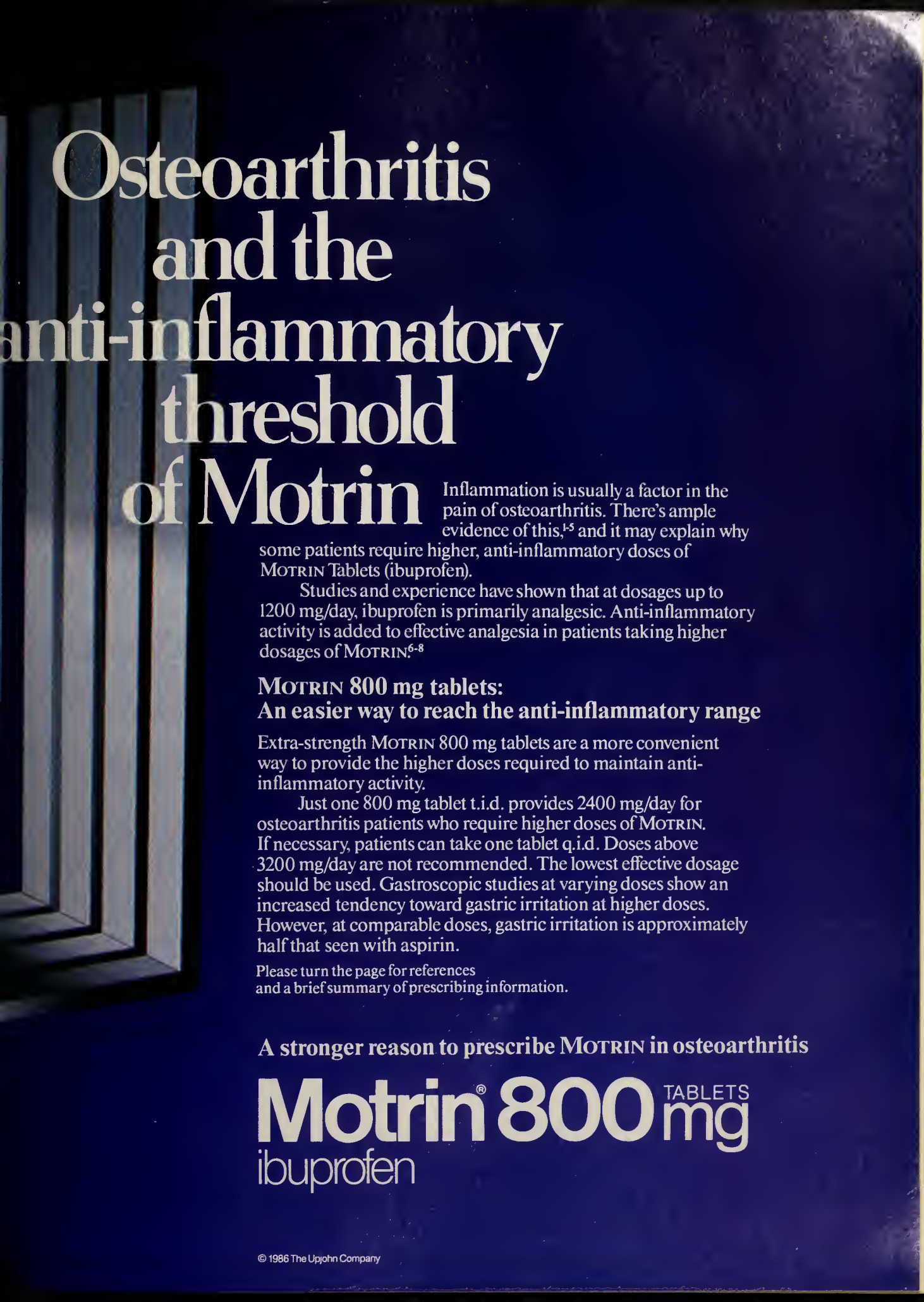

Osteoarthritis and the anti-inflammatory threshold of Motrin

Inflammation is usually a factor in the pain of osteoarthritis. There's ample evidence of this,[1-5] and it may explain why some patients require higher, anti-inflammatory doses of MOTRIN Tablets (ibuprofen).

Studies and experience have shown that at dosages up to 1200 mg/day, ibuprofen is primarily analgesic. Anti-inflammatory activity is added to effective analgesia in patients taking higher dosages of MOTRIN.[6-8]

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Just one 800 mg tablet t.i.d. provides 2400 mg/day for osteoarthritis patients who require higher doses of MOTRIN. If necessary, patients can take one tablet q.i.d. Doses above 3200 mg/day are not recommended. The lowest effective dosage should be used. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin.

Please turn the page for references and a brief summary of prescribing information.

A stronger reason to prescribe MOTRIN in osteoarthritis

Motrin® 800 mg TABLETS
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For the inflammation and the pain of osteoarthritis

Motrin® 800 mg TABLETS
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A stronger reason to prescribe MOTRIN.

References

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2. Moskowitz RW: Which comes first: Inflammation or osteoarthritis?, in Cooke TD (ed): *Clinical Patterns and Pathological Features in Osteoarthritis. J Rheumatol* (suppl 9), 1983.
3. Ehrlich GE: Osteoarthritis. *Arch Intern Med* 138:688-689, 1978.
4. Altman RD: Review of ibuprofen for osteoarthritis. *Am J Med* 77(1a):10-18, 1984.
5. Altman RD, Hochberg MC: Degenerative joint disease. *Clinics in Rheumatic Diseases* 9(3):681-686, 1983.
6. Lewis JR: Evaluation of ibuprofen (MOTRIN): A new antirheumatic agent. *JAMA* 233(4):364-365, 1975.
7. Godfrey RG, De La Cruz S: Effect of ibuprofen dosage on patient response in rheumatoid arthritis. *Arthritis Rheum* 18(2):135-137, 1975.
8. Halpern LM, Bonica JJ: Analgesics, in Modell W (ed): *Drugs of Choice.* The CV Mosby Company, 1982, pp 195-201.

MOTRIN® Tablets
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CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting AOVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished visiŏn, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAIO's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAIO's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Oiscontinuation of NSAIO therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%)– Probable Causal Relationship

GASTRDINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Oizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Oecreased appetite; **CAROIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship**

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Oepression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CAROIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINOICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Ory eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%– Causal Relationship Unknown**

GASTRDINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDDCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Oo not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

HOW SUPPLIED:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
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Plastic Surgery, board certified	17,905
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Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium: use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosoria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

JULY 1987, VOL. XLIV, NO. 7

R2D2 — Confidentiality

Marshall B. Block, M.D.

The name R2D2 caught the fancy of the world and ushered in a new view of our galaxy, yet most aren't aware that "R2D2" was actually invented approximately 50 years ago by none other than my parents, Charles and Beatrice.

Being in the "false teeth" business, Charles fabricated for dentists oral restorations out of plastic, steel and ceramics. This was a hotly contested business and any one of his 25 or so employees were potential competitors. Therefore, in order to protect his clients' identities, my father and mother devised a system of code letters and numbers. The first letter of the dentist's last name was followed by a number indicating the length of time they were clients, i.e., number 2 was an old client, number 50 a new client. It was not uncommon therefore to be at dinner and hear the following exchange, "Did L3 get his work on time?" "Yes, but M6 was angry that his was late. I think S4 is sending some of his work to others." One day while delivering packages of false teeth to dentists, I distinctly recall my father saying to me, "First go to R2 and then D2." This code exchange, a forerunner of Star Wars, sounded quite strange to outsiders, but was effective in protecting individual's identities. Because patient confidentiality is rapidly being eroded by changes in our health care system, we too have to develop a system that will offer protection to our patients.

For example, at least once or twice a week I receive a phone call from an insurance intermediary asking for the diagnosis, prognosis, and length of stay of one of my patients. They expect an answer on the phone. One recognizes that it is to the patient's, and perhaps our benefit, to give them this information, yet should we? Shouldn't we be sure the patient has given his permission to release this information to this unknown person at the other end of the line? Shouldn't we have this permission in writing? How often do we release written data to insurance companies without checking to see that we have a patient release form that is signed? How often do we have conversations regarding patients in hospital elevators when others are standing close by? How often do we mention to a colleague over coffee in the doctor's lounge about so and so patient using their names? We must constantly and consistently insist on documentation and guard against releasing patient information without written releases. Otherwise, doctor/patient confidentiality will fall by the wayside as much as "Kleenex," "Xerox" and "Scotch tape" have lost their unique identities.

Medical records are coming under increasing scrutiny by third party payors (Blue Cross-Blue Shield), intermediate reviewers (James and Company, HSAG, the Foundation), and professional and quality assurance committees at local, state and national levels (hospital, PRO and Supra-PRO organizations). Crucial information between patient and doctor will be withheld because of this

Continued on page 11

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

JULY 1987, VOL. XLIV, NO. 7

Arizona Medicine is a socioeconomic and scientific journal published monthly by The Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine.* All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by The Arizona Medical Association.

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From Our President

Robert S. Hirsch, M.D.

Are We Ozymandias?

A favorite poem, one that I first read in my undergraduate days at college, is haunting me.

I met a traveler from an antique land who said: Two vast and trunkless legs of stone stand in the desert . . . near them, on the sand, half sunk, a shattered visage lies, whose frown, and wrinkled lip, and sneer of cold command, tell that its sculptor well those passions read which yet survive, stamped on these lifeless things, the hand that mocked them, and the heart that fed: And on the pedestal these words appear: "My name is Ozymandias, King of Kings: Look on my works, Ye Mighty, and despair!" Nothing beside remains. Round the decay of that colossal wreck, boundless and bare the lone and level sands stretch far away.

Did Percy Bysshe Shelley 150 years ago have a premonition about the status of the medical profession in the 1980s? Are the legs of the profession, the day-to-day administrative workings, severed from the heart and mind, those who care, the physicians? Perhaps it stretches the simile too far to say that medicine was King of professions, and is in danger of being brought low. We may be watching our giant edifice collapse. We have given our Country the finest system of medical care in the world.

Late one night, while watching a neurosurgeon and his team quickly assemble for an emergency procedure on one of my patients, I thought to myself, "Where but in the U.S. could such service be so readily provided?" Yet, our government seems more willing to spend money to monitor us than to obtain our services. Pressures are building that may force us, like Ozymandias, to come crashing down from our exalted position.

Something has gone wrong. We have trained ourselves to be knowledgeable physicians who can respond professionally to the most intricate needs of our patients. We look at ourselves as compassionate, sympathetic, and understanding. And yet, they're after us! Who? The laymen, the patients, the consumers; they're starting a revolution! Or so, the press would have us believe.

In a recent supplement entitled "Medicine and Health," the *Wall Street Journal* reports that patients are in revolt. Why? Because the doctors and other elements of the health care system have patronized them, kept them in the dark, and treated them either as objects or as children expected to passively obey. Sir William Osler said that "The desire to take medicine is perhaps the greatest feature which distinguishes man from the animals." The lead article coun-

Continued on page 11

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Crybabies

William B. McGrath, M.D.

We are nurturing a generation of crybabies.

An article in tonight's paper described the immobolizing grief and demoralization of a man whose dog had been run over. The item concluded with a list of organizations to whom the bereaved pet owner can turn for sympathy and emotional support.

There the chap will be exhorted to "get in touch with his feelings" and to express them in handwringing tearfulness. Members of the group will be hugging him and murmuring that his pathetic exhibition need not embarrass him or subtract from his macho image.

In the original opposition to psychoanalysis there may have been a portent. The public protested against Freudian preoccupation with sexuality. Behind that emotional reaction, however, was an instinctive resistance to preoccupation itself. Interminable introspection subsequently became fashionable, going by the name of therapy.

Careless journalists and uninformed readers skidded past a crucial distinction. Painful thoughts and feelings can be *suppressed*; i.e., voluntarily excluded from awareness; or they can be *repressed*, involuntarily shut in the basement of the mind. Suppression, a deliberate and voluntary choice, is not unhealthy; repression is. The task of the professional psychotherapist is to guide the patient toward release of inchoate material that would otherwise go on fermenting and finally cause pressure and pain. Lancing the swollen unconscious is the first step in the resolution of conflict and the treatment of neurosis. The next step is *not* "acting out" behaviour, symbolic or real.

The naive presume that pent up emotions can be discharged by pounding a pillow or belting an innocent golf ball or pretending that a surrogate is real. Such is like spending counterfeit money.

The professional therapist, qua therapist, is his journeyman self. He is rather a travel agent than a paid companion. He would scoff at any notion of becoming an imaginary parent or a substitute friend or a surrogate sex partner. He is not familiar, nor is he a coin-operated dispenser of sympathy and comfort. He does not sit on the side of a patient's bed or put an encouraging arm around her shoulders.

Only the silliest and most immature therapist would resort to seductive words or suggest by kittenish foreplay that he might be the godsent answer to a maiden's prayer. He rationalizes with sick conceit that the patient will finally give up his or her symptoms out of love for him if for no one else.

Our particular profession is getting soggy and wilted. Ignorant of elementary logic many mental health workers have rendered meaningless such basic terms as depression or stress. One recently gave as an example of stress, "The breakfast toast was burned." We are up to our knees in spilt milk. Almost everyone persists in generalizing. People talk about *the* homeless, *the* handicapped, *the* Viet Nam veteran. The individual seems to have drowned in the bathos of the group.

Surely the mental and physical wounds of Viet Nam were no more heartbreaking than those of our own civil war. Any one soldier's experience has always been different from that of every other. And so with the victims of the holocaust.

Thespian lawyers scowl and pace and beat their vested bosoms in mock sincerity. They get paid for exaggerating the claims of their clients. At the end of services the milk-fed preacher calls for a lot of spin-the-bottle necking. Agapé is love for someone who doesn't deserve it. Nuts to that! Participants in group therapy commonly demand maximum self-esteem with minimum achievement.

Worst of all, or at least the nearest whipping boy, is television. It absolutely flattens the mind of the viewer. People who do creative

work must be grateful for television. It is even more effective than liquor in turning off one's own imagination.

To "suggest" annoyance the television protagonist knocks all the dishes onto the floor. The lady cop shows how street-wise she is by taking big bites out of a sandwich and using all the four-letter words. To "suggest" fear the heroine lets out a bile-curdling shriek that lasts almost as long as the commercial. To "suggest" physical attraction a topless couple writhe on the sofa with slack-jawed kisses, like the mating of vacuum cleaners. Professional boxers glare: it is safer to strike a pose than to hit an opponent. Wrestling has become the bubble gum of sports.

Surely the fiftieth fake collision or catsup gunshot wound or "explicit" portrayal of rape will not make much of an impression.

Meanwhile, to get our attention, callow youths and maidens have to outdo all these experts at theatrical display. A lad who wants use of the family car had better chain himself to the bumper. Seduced by cynical promoters, the youngsters may take part in one of those hysterical hand-holding affairs or a sit-in or they may wave crudely lettered signs in a protest march. An adolescent who is denied the latest fad or fancy might sue the parents or write a derogatory book about them.

In situations like this the amateur mental health worker, the so-called counsellor, often comes across as insufferably patronizing. It is like the inversion of an old hymn: Thou art weak and I am strong.

These paragraphs are stained with sarcasm. But just below the crust of our language there is glowing concern for the young and for people of any age who are gullible and immature. Professional and executive constraints might seem like products of prudishness. On the contrary, they condense the practical experience and the ongoing wisdom of our most respected colleagues.

If the most insignificant frustration provokes Shakespearean anguish, then what mechanisms remain for coping with the terrible crises of real life?

When nothing is left to the imagination it wastes away — and so, of course, does compassion. A further loss is equally tragic. Without imagination we no longer have individuality and independence. We settle for herding and imitation. In any field, it takes active imagination to be outstanding, original or especially creative. When we wrote that the media flatten the mind, do you see what we mean?

So, a plague on all the houses wherein television has supplanted reading and conversation and letter-writing and creative hobbies. A plague on unisex families in which the father, a mental hermaphrodite, will not or cannot command respect.

And a plague on all the schools and churches which teach that a child's every whim must be indulged. Children are given the illusion that they are lilies of the field who toil not neither do they spin. It is cruel to preach that a child just needs more demonstrative love when, in fact, he is asking for a swat on the behind.

A plague on all of us for forgetting how tough and toughening the rites of passage used to be, and how very essential they were to our becoming civilized and remaining civil. ■

William B. McGrath, M.D.

Professional Liability Adds 15 Percent to Medical Bills

A study in the *Journal of the American Medical Association* estimates that medical professional liability costs in 1984 accounted for 15 percent of total expenditures on physicians' services for that year, with much of the cost pegged to 'defensive' practice changes prompted by malpractice risk.

Roger A. Reynolds, Ph.D., of the AMA's Center for Health Policy Research, and colleagues base the study on data from the AMA Socioeconomic Monitoring System survey of liability claims and other related information for 1984. Costs associated with professional liability include insurance premiums, the cost of practice changes made in response to increasing liability risk and costs of incurring claims not covered by insurance.

The average physician's risk of incurring a malpractice claim has nearly tripled since 1980, the study reports, with indications that increases in the severity of losses have accelerated as well. The researchers say the problem is of growing public and professional concern but "to date there has been little quantitative evidence on the overall economic impact of the problem."

A 1983 report by the AMA Committee on Professional Liability placed the total costs associated with professional liability at between $15 and $40 billion. The new study notes, however, that "these estimates necessarily relied to a large degree on subjective judgment, given the limited infor-

mation available then."

The new study used two different methods to analyze the AMA data and estimate professional liability costs. One directly estimated the increases in several major components of professional liability costs in 1984; the second analyzed the impact of professional liability risk on physician fees and utilization rates for a range of services and procedures.

"Both estimates indicate that the costs . . . are substantial. In particular, the two methods yield estimates of the total cost of (professional liability) in 1984 of $31.7 billion and $12.1 billion, respectively — or approximately 15 percent of the total expenditure on physicians' services," the study says. In addition, it says, increased costs associated with professional liability from 1983 to 1984 alone are estimated to have accounted for up to 63 percent of the increase in expenditures on physicians' services.

The researchers say professional liability insurance premiums for the period studied amounted to only $3 billion and the costs of settling claims excluded from premiums $100 million. Thus, "practice changes prompted by the risk of claims accounts for a large share of total medical liability costs," they conclude.

"This study," they say, "considerably improves the reliability and narrows the bounds of (liability) cost estimates in contrast to the $15 to $40 billion range suggested by the 1983 (AMA) report." The new analyses "are necessarily less than perfectly precise," it acknowledges, but the similarity of the estimates produced "lends us confidence that they provide a general order of magnitude of medical (liability) costs."

In an accompanying editorial, Jeffrey E. Harris, M.D., Ph.D., of the Massachusetts Institute of Technology, Cambridge, and Massachusetts General Hospital, Boston, calls the new study "a giant first step in replacing loose conjecture about 'defensive medicine' with formal quantitative analysis."

Harris says the study raises the question of why the frequency and severity of malpractice claims continue to rise "if defensive medical practices have become increasingly prevalent, and if defensive medicine is truly 'defensive.' " The answer, he says, appears to be that "much of defensive medicine, as currently practiced, may not be effective risk management."

New Active Members . . .

The Arizona Medical Association welcomes the following new members:

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Obstetrics & Gynecology
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of Medicine - 1976

Mary Anna Friederich, M.D.
Obstetrics & Gynecology
5651 North 7th Street, Phoenix
University of Rochester
School of Medicine - 1957

Kevin Kroeger, M.D.
Emergency Medicine
4550 North 51st Avenue
Suite 3, Phoenix
University of Illinois
College of Medicine - 1983

Richard J. Petersen, M.D.
Radiology, Nuclear Medicine
450 West 5th Place, Mesa
Creighton University School
of Medicine - 1965

Jesse E. Pyeatte, M.D.
Ophthalmology
9425 West Bell Road, Sun City
University of Oklahoma
College of Medicine - 1955

MOHAVE

Nathan E. Beneze, M.D.
General Practice, Family Practice
1225 East Hancock, Riviera
University of Arizona
College of Medicine - 1982

PIMA

Kurt A. Schroeder, M.D.
Neurological Surgery
5182 East Farness Drive
Tucson
University of Colorado
School of Medicine -1980

Floyd J. Swenson, M.D.
Family Practice
1980 West Hospital Drive
Suite 313, Tucson
University of Minnesota
Medical School - 1958

YAVAPAI

David Shillington, M.D.
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Disease
P.O. Box 548, Cottonwood
University of Arizona
College of Medicine - 1979

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PIMA

Elliot M. Sacks, M.D.
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Health Sciences Center, Tucson
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Medicine - 1975

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Russell I. Heigh, M.D.
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State University of New York
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Health Promotion and Wellness Education In the Geriatric Population

Our patients live longer but consume more health care services and dollars. This has brought increased attention to health promotion and wellness education to postpone morbidity and control the progression of chronic diseases. Since the 1970s, community-based health promotion/wellness programs to help older persons improve the quality of their lives and maintain functional independence have proliferated. These programs flourish despite inadequate data defining effective health promotion and beneficial lifestyle intervention. Medicare HMOs are forming which cover preventive services. The public is beginning to receive wellness education from physicians despite their lack of formal training in the area. It is projected that health information may become one of the most sought health services by elderly in the future.

The College of Medicine is developing a comprehensive and coordinated program that includes: a model service delivery system integrating wellness education into geriatric medical care; the training of medical students, residents and community physicians to promote health among geriatric patients and the establishment of health promotion research through the development of a geriatric database for epidemiologic and longitudinal studies. These efforts have already led to a number of innovative programs.

Project AGE WELL, sponsored by the Brookdale Foundation and implemented by the Department of Family and Community Medicine (FCM), is a five-year longitudinal and comprehensive wellness program delivered by an interdisciplinary team serving 350 persons over age 60. Participants receive medical care either through satellite clinics in low-income housing projects staffed by the College or nursing clinic in Senior Center sites. The program has been designed to study longitudinally the impact of risk factor intervention on quality of life and chronic disease progression focusing on six areas: cardiovascular disease; cancer; depression; iatrogenic disease (drug interaction); osteoporosis; and, disease screening. AGE WELL sponsors weekly classes and provides individual counseling in exercise, nutrition, stress management, accident prevention and medication use. The program is designed to test the value of interventions such as exercise in osteoporosis, dietary fiber or fat change in cancer risk and routine pharmacy counseling to decreasing adverse drug reactions. Educational experience in gerontology is offered through AGE WELL to medical students, primary care residents and graduate students from psychology, nursing, nutrition, anthropology, pharmacy and rehabilitation.

Health-PEERS, a joint effort by the Arizona Cancer Center, FCM and the Division of Restorative Medicine (DORM), recruits and trains elderly peer counselors to deliver health information. Topics include safe physical activity to avoid accidents and dietary change to prevent cancer, cardiovascular disease and osteoporosis. Peer counselors are trained in small groups by professionals. Upon "graduation" they lead their own groups of peers to disseminate information thereby creating a "health network."

Another community-wide effort to educate the geriatric population in health promotion /wellness is the spring and fall forums coordinated by DORM. Through the well attended "Coping With Chronic Conditions" presentations, health information is delivered by specialists at the Arizona Health Sciences Center (AHSC). Annual Health Fairs for the elderly are co-sponsored both at AHSC and at Senior Centers. Students and faculty provide computerized health risk appraisal, various health screening tests, lifestyle and medication counsel-

ing, and exercise and cooking demonstrations.

The medical student curriculum makes it possible to improve both attitudes and skills in the delivery of health promotion/wellness education to geriatric patients. The "Human Behavior and Development" course during the first two years includes 10 hours focusing on aging issues with emphasis on wellness and coping with chronic conditions. The "Preparation for Clinical Medicine" course during year two teaches the role of community resources in caring for and promoting the health of geriatric patients and an appreciation for the role of physicians in health promotion/disease prevention. Fourth-year selectives are offered in ambulatory geriatric medicine. Students may become involved in AGE WELL and Health-PEERS. Residents in family practice and preventive medicine participate in wellness teaching through assessment clinics, supervising exercise testing of geriatric patients and health screening routinely offered in the outpatient clinics. The Faculty Development program offers workshops to community-based and College preceptors on teaching geriatric patients about wellness and on motivating students and residents to work creatively with older patients to promote health.

Medical education can and must offer students and residents in geriatric medicine more than just basic skills in the diagnosis and management of illnesses. The health care system can and must offer geriatric patients more than just diagnoses and treatment for their health problems. The traditional medical education model is expanding to include health promotion. The College of Medicine is building a wellness education program based on sound research and an adequate database.

Our graduates should have no difficulty writing lifestyle prescriptions that will lead to healthy added years for the geriatric population. ■

Evan W. Kligman, M.D.
Assistant Professor
Department of Family and Community Medicine

Anthony F. Vuturo, M.D., M.P.H.
Professor and Head
Department of Family and Community Medicine

Louis J. Kettel, M.D.
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Phone Pirates Threaten Arizona Physicians

It's only a matter of time before a phone scam that's cost physicians across the country millions of dollars makes its way to Arizona, AT&T security officials predict.

It's hit Texas and California, and unless Arizona's physicians take precautions quickly, they could find themselves in the shoes of doctors from other parts of America who have received phone bills in multiple thousands of dollars.

The scam is based on a machine called a call diverter, which some physicians use to connect after-hours office calls to their answering services. But diverters have an electronic design flaw which allows unscrupulous persons known as phone pirates to bill their calls to the doctor's office phone.

According to AT&T fraud specialist Pat C. DeChirico, the fraud works like this:

The pirate calls his doctor after hours. The call diverter links the pirate to an outgoing line which connects to the answering service. When the answering service hangs up, the outgoing line returns to dial tone. The pirate can then call anywhere in the world, on the doctor's phone.

"The really dangerous thing," DeChirico said, "is that a significant portion of these pirate calls are to teleconferencing bridges, which means up to 15 parties can be on the line for hours, all at the physician's expense. The expense mounts up very quickly with that many people on the line."

The cheaper the diverter, the more likely it is that a pirate can fraudulently use the physician's phone line.

There are several ways that physicians can protect themselves, DeChirico said, "but don't kid yourself. They all cost money. They just don't cost as much money as the phone fraud could cost."

The first and best way is, if possible, to throw the diverter in the trash and switch to the local telephone company's "call forwarding" system. With call forwarding, the line disconnects automatically when the answering service operator hangs up, and it does not return to dial tone. In Arizona, Mountain Bell says the call forwarding option costs businesses no more than $2.37 per month.

The obvious problem with call forwarding is that it is not available in all the rural areas of Arizona. If it is not available, DeChirico said, there are still ways that a physician can protect his phone lines after hours.

"There are two lines attached to a diverter," he said. "There's an incoming line that patients, and pirates, use to call the doctor's office. Then there's the outgoing line that connects the diverter with the answering service. The outgoing line *must* be restricted."

Any local phone company ought to have technicians who can restrict a business customer's outgoing line so that long distance or operator assisted calls cannot be made, DeChirico said.

That takes care of the immediate problem, he said, but more should be done to resolve the long range problem of the flaws in the manufacture of the diverters.

"We need physicians to contact the Federal Communications Commission (through which all interstate communications equipment must be registered) and ask the FCC to pressure the manufacturers to correct the flaws. Without a lot of input from physicians, and from other professionals who use answering services, we think it will take quite a while for the manufacturers to do anything."

A large group of California physicians, including those whose phones were used by pirates, have already petitioned the FCC to work for improvements in the manufacturing process.

"We're trying to get the word out to all professionals who may be affected by this fraud," DeChirico said. "We need to work together." ■

Free Marketing Guide

Arizona physicians can now order a product physicians everywhere have needed for a long time — a no-nonsense guide to marketing and communications decisions to support their practices.

Titled "96 Marketing Ideas for Physicians," the 24-page booklet gives advice on patient research, marketing, copywriting, communicating with older patients, graphics, color, type, phone book ads, and working with consultants.

The booklet, produced by two Sacramento marketing and advertising companies, is available free of charge to physicians and health care professionals. Write to Dept. 96, Dane Henas Design, 1734 34th St., Sacramento, CA 95816, and enclose $2.00 to cover postage and handling.

Editor's Message
(Continued from page 1)

intrusion, and this will hurt the therapeutic potential which we have to offer. If patients won't reveal their sexual preferences for fear of exposure, how can we diagnose and search for activity-related disease? If patients don't tell us their emotional turmoil for fear of it being disclosed, how can we truly offer any help to these troubled individuals?

The whole issue of "patient respect" needs to be addressed in light of our changing health care environment. Exposing the present and future deleterious effects of this erosion needs to be undertaken at all levels of care, locally and nationally. We should be at the forefront of this battle as patient advocates. ■

Marshall B. Block, M.D., Editor

President's Message
(Continued from page 2)

ters with the statement: "No animal would, in the name of therapy allow another to do what man has allowed his physicians to do to him over the centuries. They have bled him by the gallon, purged him senseless, and so forth. Sometimes, they live, despite all this assistance." And further painting a word picture of patients rising to defend themselves against doctors and hospitals, a description of the activities and attitudes of a veteran of the "Health Care Wars" is provided. He is a heart patient, a "semi-pro-pain-in-the-neck" for whom passive acceptance is not a long suit. The description goes on of a man who has summarily fired physicians, signed out of hospitals, and walked out of offices, to assert his consumer rights and to command attention from his providers. According to this gentleman, a tough, demanding demeanor is the only way to get noticed.

Is this really what is happening? Are we seeing a sea of change in patient attitudes? Have physicians declined so far in their ability to inspire confidence and trust, that they must be so shockingly put in their place? Will the "semi-pro-pain-in-the-neck" be the bemedalled hero of a Wall Street tickertape parade when the insouciant, depraved medical establishment, as it has been called, is finally conquered and led off to its just desserts?

Newsweek puts us in our place in the January 26th issue. Above the picture of the capped and masked face of a doctor appeared the title, "The Revolution in Medicine." pages 40-74, an unusually large amount of space for a feature article in such a publication, examines the profession from many points of view. Most are not flattering. Among some of the more striking faults attributed to physicians are greed and lack of credibility. Hence, the statement: "What bothers doctors and hospitals is not that they cannot make money on Medicare—they can—but that, in the wake of DRGs, it has stopped being a pot of gold."

This is said in the context of the writer's acceptance of the idea that DRGs will solve problems. A congratulatory adulation of an unproved tenet, a belief that the medical profession does not uniformly share. But it is another demonstration of the public's willingness to accept negative comments about our profession for almost any stand we take.

The article also attacks the credibility and community conscience of doctors by saying that, just as one would not trust a panel of journalists to decide whether special protection should be granted to freedom of the press, even though journalists are experts in this subject, when it comes to public health policy, the medical community's view must be approached with equal skepticism.

What comes from this laborious study by *Newsweek* of today's medicine in the United States is a conclusion that a nationalized system would be best to flatten cost and improve access. But in comparing care in various countries, the writer finds that in the United States, care is the best. He admits that of the socialized nations, only Canada has medicine equal to ours, and its conversion from the free enterprise system is the most recent. European socialized approaches are possible, in part, because the money-hungry American system produces breakthroughs that others can buy or duplicate. So, at least, the Devil is given his due: some acknowledgement is granted, despite all of our

reputed avarice, egotism, lack of caring, and condescension to the "semi-pro-pain-in-the-neck," that American medicine is still the best. Indeed! How gratifying! But how can it remain the best, when the media, the Congress, and the press demand that physicians change completely in ways yet unspecified, and that the whole game of health care be played with rules subject to change in a twinkling or at a whim?

If American medicine is to continue to set the standard for the world to emulate, we must not fall prey to unproved changes parading as remedies for the system. In this regard, several issues must be addressed.

First, we must have credibility in the scientific advice we give to our individual patients, and to the public at large. An example of conflicting recommendations that can only confuse the public is what is termed editorially in the April issue of the *Annals of Internal Medicine* the "Cholesterol Saga." The authors of a scientific article, Taylor, et. al., writing on cholesterol reduction and life expectancy, make various assessments of the danger as related to age, cholesterol level, and other risk factors. The increase in life expectancy so calculated varies with background risk, and is anywhere from three days to 18 months. What with all the publicity about cholesterol, the fish oils, exercise, diet, smoking, alcohol, and so on, the public is confused. Meg Greenfield, editorializing in *Newsweek* has said, "What new findings overturn are other new findings just barely established in the understandably addled public mind. This phenomenon has us forever importuned to take huge doses of whatever it is we had just succeeded, with much personal agony, in eliminating from our diet. By now, the public suspects that what is banned today, is likely to be administered intravenously in all the best clinics tomorrow." Thus, to our recommendations, the public can say "This too, shall pass."

Commenting on the Taylor article, Marshall Becker, the editorialist, concludes that our most sensible public health recommendation should be moderation in all things. The point I raise is that individual discoveries and so-called breakthroughs should be iced until they become fact. Medicine by press conference should be discouraged; when announcements are made, they should be heavily qualified by statements about their applicability to the population at large. As Sir William Osler said: "In the life of every successful physician, there comes the temptation to toy with the Delilah of the press. There are times when she may be courted with satisfaction, but beware! Sooner, or later, she is sure to play the harlot and has left many a man shorn of his strength, which is the confidence of his professional brethren."

Secondly, I believe that we must return to being a profession. It's a good idea to remind ourselves periodically of just how that term is defined: "A calling requiring specialized knowledge and often long and intensive preparation . . . maintaining . . . high standards of achievement and conduct." That definition sets us apart from the other types of endeavor. If we permit ourselves to be packaged and marketed by the huxterism of companies, corporations, and mega-businesses, we cannot hope to have the dignity and command the respect that learned professionals ought to have. In my opinion, it is essential that we stop the practice of giving credence to untried health businesses by signing our names, and with them, our reputations, to lists of providers. Investigate, question, demur, think—those businesses need our signatures. They cannot survive without them. We need be in no haste to give them acceptance. If we would but keep our poise, and pause to consider the many "join-up" proposals presented to us, we would see the weakness inherent in many. Our reputations can only be hurt by aligning ourselves with a multiplicity of failed enterprises.

I could go on with my list, but I think it suffices to say that the crux of medical practice will continue to be communication in a one-to-one relationship between doctor and patient. John Steinbeck said, "The medical profession is unconsciously irritated by lay knowledge." We must not let that perception be the truth. Let us try to bury those terms "provider" and "consumer." Maybe that's alright in the grocery business, but not in the caring practice of quality medicine.

Unquestionably, there are monumental problems. Oh, yes, we hear that things change; we musn't be dinosaurs, even though the dim did last for millions of years. Many colleagues say that they make very basic decisions in their practices based on the advice of financial consultants. They say that these decisions are sophisticated, that they reflect the realities of the changing times. What could lend more belief to the widespread feeling that money is our prime motivator than this type of rationalization?

In confronting today's problems, can we find solace and strength in the wisdom of our professional predecessors? Heraclitus said in 513 B.C. that "Doctors cut, burn and torture the sick, and then demand of them an undeserved fee for such services." We can't very well trade on that

reputation. Hammurabi, about 2000 B.C. anticipated DRGs when, in his writings, he recommended that "For treating a gentleman's servant, a doctor should receive 2 sheckles of silver from the master." I'm not sure we want that type of structured fees. An anonymous Latin poem says:

Three shapes a doctor wears—
At first we hail the Angel;
Then the God, if he prevail.
Last, when the cure complete,
He asks his fee,
A hideous demon he appears to be.

What better could express the general feeling about reimbursing physicians, no matter by what system it be done?

More seriously, we should heed the advice of Albert Schweitzer. "It is our duty to remember at all times that medicine is not only a science, but the art of letting our own individuality interact with the individuality of the patient." I, for one, like that. That word, individuality—that's the core! That's why I went into this profession in the first place. It's too precious to give up. They need us out there, those patients. But they need us with all the scientific wisdom we can muster, balanced with large doses of understanding, compassion, and, on occasion, even . . . paternalism. Neither the insurance company, the administrator of the hospital, nor the "Alternative Delivery System" can help them when they are sick, only the doctor can. They know it. We are the final common pathway in all health delivery systems. Let us be confident of our worth. Let that be our beacon in the so called sea of change.

As Sir George Pickering reminds us: "Unless the doctor is utterly devoted to his patients and prepared to take immense trouble to understand their problems, he is inferior to a machine. It is only by virtue of that rather intangible and neglected quality, his attitude of mind as expressed by his devotion to his patient, the real ethos of medicine, that he becomes superior."

In closing, I would like to express my gratitude to my predecessors in this office for the foundation of wisdom and insight they have brought to it. I hope that I will be able to add a little to it and pass it on to my successor. Thank you for granting me the honor of serving you in this Presidency. ■

Robert S. Hirsch, M.D.

Inaugural Address of Robert S. Hirsch, M.D., President, Arizona Medical Association — Annual Meeting June 5, 1987, The Pointe at South Mountain, Phoenix, Arizona.

To The Editor:

I enjoy the section in *Arizona Medicine* entitled "Physicians in the News." It not only provides some local color, but it is also an excellent way to learn what our colleagues are doing and have achieved.

A friend of mine was recently appointed to serve on the American Board of his specialty. Understand, he didn't just get his boards, he is *on* the Board. That's a big-time appointment for a "local boy"—an honor usually accorded academic and institution-based physicians. The announcement that appeared in this journal, and his county society periodical was just that; an announcement. Anything beyond that would have embarrassed him and would have seemed out of place.

Contrast that with some of the "commercials" that have obviously been submitted "for publication" in the same section. Review the April, 1987 issue. I know there is a fine line between providing information and embellishing it a little, or a lot. Some of the items submitted are obviously not prepared by the physician herself or himself, but rather by someone whose job it is to "market" that physician. But, they should do their marketing elsewhere. "Physicians in the News" should be for information. Ego support can be purchased on the open market, or obtained at home.

The battle over advertising has been fought and lost, and was recently debated in one of our county society journals. I accept that defeat, reluctantly. You have only to witness what has happened to the once proud field of ophthalmology. There is not much dignity when someone has to proclaim, "I am the greatest," or when new office openings feature drawings for expense-paid trips to gambling casinos. Professionalism? Forget it. Ninety-five percent of doctors labor quietly, observe changes they often find disgusting, and wonder "what is going on here?"

Thank you for "Physicians in the News," and for all of your efforts. ■

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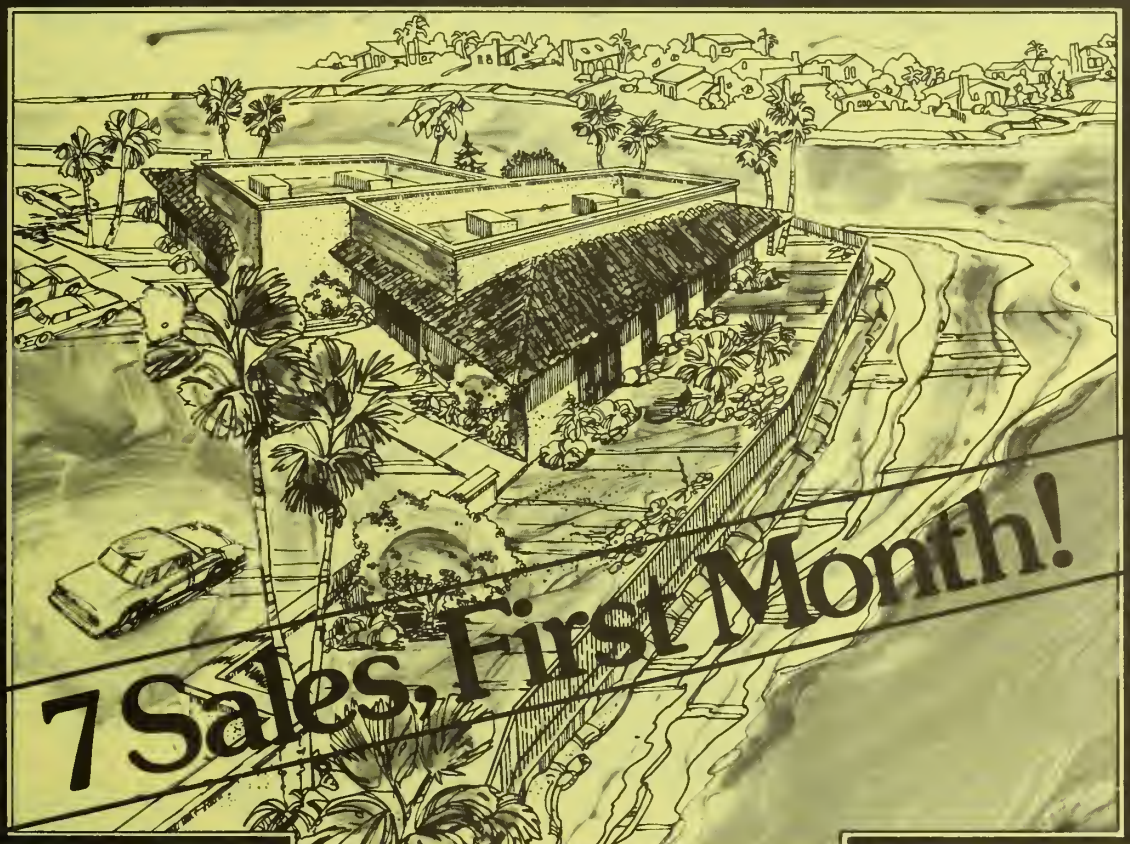

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AIR FORCE

Farewell

Outgoing ArMA President Neil O. Ward, M.D., of Phoenix responded to a "birthday request" from Board Attorney Edward Jacobson, Esq., and gave his farewell remarks from the balcony of the Board Meeting room.

ArMA's 96th Annual Meeting

The 96th Annual Meeting of The Arizona Medical Association's House of Delegates was held June 4, 5 and 6 at The Pointe at South Mountain, Phoenix. New officers and delegates to The American Medical Association were elected, as were alternate AMA delegates and members of the ArMA Board of Directors.

Auxiliary

The report on activities and accomplishments of the ArMA Auxiliary during the past year was given by Auxiliary President Jean Dew of Tucson.

Greetings

ArMA's new President, Robert S. Hirsch, M.D., of Tucson greeted members of the ArMA House of Delegates during their 1987 Annual Meeting. Seated are outgoing President Neil O. Ward, M.D., left, and Parliamentarian Charles Henderson, M.D., center.

Robert S. Hirsch, M.D., of Tucson was installed as ArMA's 1987-88 President; **Richard L. Collins, M.D.**, of Scottsdale was elected President-Elect; **Mark Ivey, Jr., M.D.** of Payson was elected Vice President; **Robert J. Brooks, M.D.**, of Tucson was elected Treasurer; and **Richard O. Flynn, M.D.**, of Tempe was elected Vice-Speaker of the House.

AMA Delegates elected were **Neopito L. Robles, M.D.**, of Tucson, **Edward Sattenspiel, M.D.**, of Phoenix, and **Richard D. Zonis, M.D.**, of Scottsdale. Alternate AMA Delegates elected were **Paul T. Lenio, M.D.**, of Sierra Vista, **Philip Levy, M.D.**, of Phoenix, and **Walter K. Sosey, M.D.**, of Lake Havasu City.

Complete information about action taken by the Executive Committee, the Board of Directors and the House of Delegates on resolutions and Bylaw amendments is covered in a Medical Memo sent to all members of The Arizona Medical Association.

Legislature

Tort reform legislation approved, defeated and ready to return next year was reviewed by State Legislator Jim Meredith of Phoenix.

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Overmedication of Low-weight Elderly

Low body weight, as well as advancing age, are key risk factors for patient overmedication and drug toxicity, but physicians may not be adjusting drug doses for these considerations, says a study in May's *Archives of Internal Medicine*. Edward W. Campion, M.D., of Massachusetts General Hospital and Harvard Medical School, Boston, and colleagues studied three drugs prescribed for 1,800 patients, average age 72 years, analyzing weight, age and dose. For all three, mean milligram-per-kilogram dosages rose sharply as patient weight declined, says the study, and "there was no trend seen toward reducing doses for older patients." This problem "appears to result from standard dose regimens being prescribed by habit, with little adjustment for individual patients," the study says. Doctors, it says, "must recognize the need to reduce drug doses for their low-weight, elderly patients."

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Peripheral Vascular Surgery Safe In Older Patients

There is debate over the risks and benefits of many types of surgery in the elderly, including peripheral vascular operations. A study in May's *Archives of Surgery* says, however, that not only can such procedures be performed safely in elderly patients, but that aggressive revascularization is a cost-effective way of treating limb-threatening ischemia (insufficient blood flow) caused by arteriosclerotic vascular disease. Thomas H. Cogbill, M.D., of the Gundersen Clinic, La Crosse, Wisconsin, Lutheran Hospital, and colleagues studied 114 patients age 80 and older who underwent 119 peripheral arterial procedures over a seven-year period. Overall mortality was low, except for certain emergency procedures. Of 48 long-term survivors, 65 percent were living at home and 28 were fully ambulatory. "Pheripheral arterial reconstruction in patients 80 years of age and older can be performed safely with excellent long-term survival and quality of life," the study concludes.

Physicians in the News

Paul Dempsey, M.D.

Tucson plastic surgeon **Paul Dempsey, M.D.**, recently returned from a very different kind of travel experience — 10 days as part of a 15-member volunteer reconstructive surgical team for poverty stricken children in the Peruvian city of Arequipa.

The million-resident city itself wasn't all that different from home, Dr. Dempsey said. Located 7,500 feet above sea level in southern Peru, it is sunny and arid and has much of the desert atmosphere of southern Arizona.

The medical experience, however, was totally new, he said.

For starters, the health care system is different. There is no Medicaid or public health financial assistance, and the hospital they worked in has limited resources to provide care for those who cannot pay. Because many of the people are poor, medical treatment is frequently delayed.

"Many of the children we treated as teenagers had problems we would have expected to have been taken care of years ago, when they were small children, if they had been in the States," Dr. Dempsey said.

The patients treated by the volunteer team were screened from a waiting list selected by last year's volunteer team, he said, and most of the children treated had one of two major problems. Some had cleft lips or cleft palates which made it extremely difficult for them to eat or speak, not to mention cosmetic or psychological problems. Others were serious burn victims with severe scars which made walking or using their arms almost impossible.

During eight days of surgery, Dr. Dempsey treated 40 patients. The surgical team worked from 7:30 in the morning until 8 or 9:00 at night.

Like the system and the patients, the working conditions were also very different. "There were no books or continuing medical training courses for the resident medical staff," Dr. Dempsey said, "and for us, there was no equipment or surgical instruments. Most amazing, there was no electricity to provide light after dark."

The surgical team members brought their own instruments, anesthesia and anesthetic equipment, other medical equipment, and "at night, we worked under the spotlights we brought with us," Dr. Dempsey said.

"It was difficult, but we developed a terrific esprit de corps, great teamwork," he said.

The team included the chief of plastic surgery at Stanford University's College of Medicine, a resident plastic surgeon, surgical and recovery room nurses, pediatricians, a social worker/translator and an equipment man.

In fact, Dr. Dempsey said, the camaraderie was so good that "at least a segment" of the team is trying to stay together for future volunteer medical trips to third world countries. Destination options include a return to southern Peru, northern Peru, Chile, Honduras, the Philippines, Africa or Jamaica, but the Amazon jungles of Equador are most likely for the next trip, Dr. Dempsey thinks.

"I'm planning to go on a volunteer trip like this once a year," he said. "Although I'd like to, I really can't do more because of the demands of my practice at home."

The trips are sponsored by Interplast, a non-profit organization which works with representatives in developing nations around the world to provide free medical care to indigent children.

Based at the Stanford University College of Medicine, the organization provides medical teams including pediatricians, cardiothoracic and plastic surgeons. Most team members come from the Southern California medical community, but occasional volunteers from other parts of the country are included.

His first involvement in the volunteer medical mission to third world nations was "a fluke," Dr. Dempsey said.

"Through a friend at Stanford I met their chief of plastic surgery several years ago," he said. "I ran into him a few months ago at the annual meeting of the California plastic surgery specialty society which was held here in Tucson, at Ventana Canyon. He had just had someone drop out of the team scheduled to go to Peru and was looking to fill the vacancy. He asked if I'd be interested and I jumped at the chance."

The program is funded by private donations from foundations, individuals, corporations and civic associations such as Rotary International. In fact, Dr. Dempsey ended up staying with a member of the local city Rotary club while he was in Arequipa.

"It was a challenge, but I learned to speak much better Spanish while I was there," he said.

Clifford J. Harris, M.D.

Clifford J. Harris, M.D., has been elected vice president to the Board of Regents of the American College of Physician Executives during the College's 12th National Conference on Health Care Leadership and Management in Toronto, Ontario, Canada.

Dr. Harris, Senior Vice President and Medical Director of the southwest division of CIGNA Healthplan of Arizona, was elected to the College's Board of Regents in 1985. He joined in 1982 and was awarded Fellowship status in 1983.

The American College of Physician Executives is the only national professional accrediting association which recognizes and certifies physicians who have demonstrated high achievement in health care leadership and management.

Dr. Harris, a member of the Arizona Medical Association's House of Delegates, has spent over two decades as a key health care association administrator. He served as chief of the department of medicine at Southside District Hospital, Mesa, from 1965 through 1967; became chief of the department of medicine at Mesa Lutheran Hospital in 1966; and was elected president-elect and president of staff at Southside District Hospital in 1968 and 1969.

In 1969 Dr. Harris became president of Health Maintenance Associates, a position he held until 1974 when he became Medical Director for HMA. During 1977 and 1978 he held both positions concurrently.

Dr. Harris was named Medical Director of INA Healthplan of Arizona in 1978; INA's Western Regional Medical Director in 1980; and in 1982 he became Senior Vice President for Medical Affairs for CIGNA.

Dr. Harris serves as consultant to Desert Samaritan Hospital, Mesa Lutheran Hospital, Boswell Memorial Hospital and Good Samaritan Hospital.

He is certified in internal medicine, hematology and oncology, and is licensed to practice in Illinois and California as well as Arizona.

Rhema Sayers, M.D.

Douglas obstetrician **Rhema Sayers, M.D.**, has been named Lady of the Year by Beta Sigma Phi sorority in recognition of her service to the community as the

Continued on page 22

Do Doctors Recognize Child Sexual Abuse?

Physicians need to improve their knowledge and skills in diagnosing child sexual abuse if the problem and its consequences are to be minimized, a study in a recent *American Journal of Diseases of Children*, says. Stephanie Landson, of the Ohio State University College of Medicine, and colleagues surveyed 129 pediatricians, family practitioners and others on their knowledge and attitudes about sexual abuse. While individual characteristics affected diagnostic skills and reporting behavior, overall, the study found the respondents had "limited knowledge of and attitudes about sexual abuse. The lack of knowledge these physicians display about prepubescent female anatomy and the association of venereal diseases with sexual abuse decreases their recognition and reporting of sexual abuse." Commenting editorially, Helen L. Britton, M.D., of the University of Arizona Health Sciences Center, Tucson, says it is "imperative that physicians in all areas of medicine become familiar with the problems of both the abused and the abuser."

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Dr. Sayers
(Continued from page 20)

only OB/GYN in town and her work on the boards of the Domestic Crisis Shelter, the Southeast Arizona Medical Center and the Arizona Health Education Center.

Dr. Sayers, a graduate of the University of Connecticut School of Medicine, is also responsible for starting a visiting clinic in the Elfrida area, sponsoring a winter weight loss program at the Douglas Recreation Center and sponsoring a local soccer team.

She has also been active as preceptor of the University of Arizona and the Cochise College nursing school.

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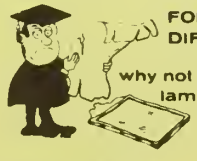

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Carpal Tunnel Syndrome in Grocery Checkers

A Cluster of a Work-Related Illness

SCOTT BARNHART, MD, *and* LINDA ROSENSTOCK, MD, MPH, *Seattle*

Grocery checkers must use a high level of repetitive motion in the course of their work. We report a cluster of seven cases of the carpal tunnel syndrome felt to be due to the excessive use of repetitive motion. Each of the grocery checkers had no other identifiable risk factors, and hand pain, physical examination abnormalities and prolonged median nerve sensory latencies had developed that were consistent with the diagnosis of the carpal tunnel syndrome. This cluster of cases, the relation of the history of their disorder to time at work and a review of the literature suggest that grocery checkers, because of their excessively repetitive tasks, are at increased risk for the carpal tunnel syndrome.

(Barnhart S, Rosenstock L: Carpal tunnel syndrome in grocery checkers—A cluster of a work-related illness. West J Med 1987 Jul; 147:37-40)

The clustering of cases with common workplace exposures may signal the presence of a work-related disorder. The recognition of clusters of cases has led to the identification of a number of work-related illnesses, including small-cell carcinoma due to exposure to bischloromethyl ether and neurogenic bladder due to exposure to dimethylaminopropionitrile.[1,2] We report a cluster of seven cases of the carpal tunnel syndrome among grocery checkers and provide a brief review of the literature implicating repetitive motion as a risk factor for the development of this disorder.

The carpal tunnel syndrome is one of pain and weakness of the hands resulting from compression of the median nerve as it passes through the carpal tunnel. Untreated, it may result in chronic pain, weakness and significant impairment in the functioning of the affected hand.

As early as 1911, Ramsey Hunt raised the question as to whether atrophy of the median nerve could be associated with repeated flexion and extension at the wrist.[3] Since that time several studies have associated the carpal tunnel syndrome with repeated wrist flexion and extension.[4-6] This syndrome has also been associated with a number of other risk factors including hypothyroidism, rheumatoid arthritis, a history of gynecologic operations, the use of birth control pills, wrist fractures, acromegaly, diabetes mellitus, amyloidosis and neuromas.[4,7]

There are more than 200,000 grocery checkers in the United States, and the retail industry employs more than 25 million workers. Grocery checking involves highly repetitive tasks. Checkers handle more than 500 items per hour and fill as many as 80 bags per hour. Over an eight-hour shift, they may handle more than 2,720 kg (6,000 lb) of groceries.[8] This extraordinary use of repetitive motion may place grocery checkers at increased risk for a number of neurologic and musculoskeletal disorders including the carpal tunnel syndrome, tendinitis and low back pain. The cluster of seven cases of the carpal tunnel syndrome among grocery checkers described below is felt to represent the consequences of the use of excessively repetitive motion among the members of this common trade.

Patients and Methods

In a retrospective review of 943 patients evaluated in the Harborview Occupational Medicine Clinic (Seattle), we identified 26 cases of diagnosed carpal tunnel syndrome. Among the 14 cases occurring in women, 8 were grocery checkers (7 of whom were members of the United Food and Commercial Workers Local 1105; membership includes about 1,800 female checkers). One case was eliminated from the discussion because of concomitant Raynaud's phenomenon, raising the possibility of a systemic illness unrelated to occupational exposure. The charts of the seven remaining patients were reviewed for demographic information, duration and type of work practice, clinical symptoms, physical examination abnormalities including Tinel's and Phalen's signs and nerve conduction velocity testing for the sensory latencies across the wrist. Tinel's sign was defined as pain or tingling in the hand following tapping over the median nerve at the wrist crease, and Phalen's sign was defined as pain or tingling in the hand following flexion at the wrist for a minimum of 60 seconds.

Results

A summary of the exposures for the seven cases reported below is given in Table 1. The mean age was 43 years, mean hours worked per week 32 hours and mean length in trade 12 years.

The presence of signs and symptoms and the results of electrodiagnostic studies are shown in Table 2. Four of the seven complained of night pain, and all had a positive Phalen's sign in the affected wrist. Each patient had an antidromic

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TABLE 1.—*Age and Exposure of 7 Grocery Checkers to Repetitive Motion Tasks*

Case	Age, yr	Average Hours/Week	Years in Trade, Number
1	26	35	10
2	34	35	4
3	63	29	29
4	49	32	9
5	55	30	12
6	29	36	7
7	46	32	15
Total*	43±14	32±3	12±8

*± Standard deviation.

median nerve sensory latency that was greater than 2 standard deviations above the predicted normal of 3.2 milliseconds (standard deviation [SD] 0.2). In most of the cases, ulnar nerve sensory latencies were measured for comparison and, except for one case, were within the normal range.

Reports of Cases

Case 1. The patient, a 26-year-old woman with ten years' employment as a supermarket checker, presented with a history of numbness and tingling in her right hand for one year that had become apparent and worsened following the introduction of an electronic checkout scanner in her store. The numbness and tingling were aggravated while she was at work, and she frequently was awakened at night with numbness and tingling in the affected hand. Her medical history was unremarkable, and she was taking no medications. The only abnormalities noted on physical examination were positive Tinel's and Phalen's signs on the right. Antidromic right median sensory latency was 5.3 ms, right ulnar sensory latency was 3.8 ms and left median sensory latency was 3.2 ms.

A diagnosis of a right carpal tunnel syndrome was made, and the patient was given a wrist splint that she wore 24 hours per day while continuing to work. After beginning to wear the splint, she noted a substantial decrease in her symptoms. Follow-up measurement of her right median sensory latency at one, two and six months has shown a decrease from 5.3 to 4.8, 4.2 and 3.5 ms, respectively.

Case 2. A 34-year-old woman presented with pain, numbness and tingling in both hands, though more in the right than in the left, for about 16 months. She had worked as a supermarket checker for 4 years and for the past 18 months had been using an electronic scanning cashier. Her symptoms tended to improve over weekends and vacations. The findings of a physical examination were remarkable for the presence of a Phalen's sign and the absence of a Tinel's sign in both hands. There was no evidence of thenar muscle atrophy and distal sensation was normal. Her right and left median sensory latencies were 4.0 and 3.2 ms, respectively, with normal ulnar sensory latencies. A diagnosis of a right carpal tunnel syndrome was made and she was given a wrist splint.

Case 3. A 63-year-old supermarket checker who had retired two weeks previously presented with numbness and pain in both hands. The pain and numbness began almost 17 years earlier. The symptoms waxed and waned but recently had become much worse with the introduction of electronic scanners in her store and the attendant increase in the use of her hands. On physical examination she had mild atrophy of the thenar muscles, decreased vibratory sensation distally on the hands and feet, a negative Tinel's sign and a positive Phalen's sign bilaterally. Right and left median sensory latencies were 5.5 and 7.5 ms, respectively. Sensory latencies of the right and left ulnar nerves were 3.3 and 3.1 ms (normal, 3.2 ± 0.2 SD), respectively. A diagnosis of a bilateral carpal tunnel syndrome was made. She elected to have a surgical release of both flexor retinacula, resulting in resolution of her symptoms.

Case 4. The patient, a 49-year-old supermarket checker, presented with complaints of pain and soreness in her hands, arms, neck and lower back. These pains were all aggravated by her work as a checker. In addition, she complained of her arms going numb at night for the past two years. Her medical history was remarkable for a bilateral tubal ligation in 1974, and on physical examination she had a positive Phalen's sign on the right. On nerve conduction velocity testing, she had a right and left median sensory latency of 3.9 and 3.2 ms, respectively. Right ulnar sensory latency was 2.8 ms. A diagnosis of a right carpal tunnel syndrome was made.

Treatment was begun with a cockup splint on the right hand for 24 hours a day. The patient was then taken off work for one month, during which her symptoms resolved entirely and her right median sensory latency decreased to 3.5 ms.

Case 5. The patient, a 55-year-old checker, presented with pain in her left hand for two years. The pain was located in her first three fingers and was accompanied by intermittent numbness. Her job as a checker involved keying in the prices with her right hand and moving groceries with her left hand. No abnormalities were found on physical examination, with the

TABLE 2.—*Signs, Symptoms and Median Nerve Sensory Latencies of 7 Grocery Checkers With the Carpal Tunnel Syndrome*

Case	Involved Hand	Hand Pain or Numbness	Night Pain	Tinel's Sign	Phalen's Sign	Median Sensory Latencies, ms	
						Right	Left
1	Right	Yes	No	+	+	5.3	3.2
2	Right	Yes	No	–	+	4.0	3.2
3	Both	Yes	Yes	–	+	5.5	7.5
4	Right	Yes	Yes	–	+	3.9	3.2
5	Both	Yes	Yes	–	+	4.5	6.4
6	Left	Yes	Yes	–	–	3.7	4.4
7	Right	Yes	No	–	+	4.2	3.5

+ = positive, – = negative

exception of a positive Phalen's sign bilaterally. Nerve conduction velocity testing showed a right and left median sensory latency of 4.5 and 6.4 ms, respectively. The right and left ulnar sensory latencies were normal. A diagnosis of a bilateral carpal tunnel syndrome was made.

The patient was taken off work and both her arms were placed in cockup splints for 24 hours per day. After five months her symptoms resolved completely, and her right and left median sensory latencies were both 4.5 ms.

CASE 6. A 29-year-old checker presented for evaluation of pain and aching of her left hand. She worked approximately 8 hours per day, 30 to 40 hours per week. She presented for evaluation two months after the onset of her initial symptoms, with aching and tingling in her left hand. The findings of a physical examination were unremarkable. On nerve conduction velocity testing, she had a right and left sensory latency of 3.7 and 4.4 ms, respectively.

A left carpal tunnel syndrome was diagnosed, and she was treated with the administration of ibuprofen in addition to a cockup splint. She returned to work using the splint. After one month she indicated that her hand felt worse. She was taken off work, and her symptoms improved over six weeks. Follow-up nerve conduction velocity testing showed a decrease in the left median sensory latency from 4.4 to 3.7 ms.

CASE 7. The patient, a 46-year-old supermarket checker, presented with increasing pain and numbness and decreasing grip strength of the right hand over the past year. She frequently was awakened from sleep with pain in her right hand and had the recent onset of poor coordination of her right hand and decreased strength. Her history is remarkable for a rotator cuff tendinitis of her right shoulder two years previously, a right lateral epicondylitis one year previously and a bilateral tubal ligation in 1974. On physical examination she had mild right epicondylar tenderness and a positive Phalen's sign on the right.

Her right and left median sensory latencies were 4.2 and 3.5 ms, respectively, and right and left ulnar nerve sensory latencies were 3.4 and 3.2 ms, respectively. A diagnosis of a right carpal tunnel syndrome was made, and she was given a right cockup splint.

Discussion

The carpal tunnel syndrome is felt to be induced or aggravated by any process that compresses the median nerve as it passes through the narrow confined space of the carpal tunnel. Repetitive flexion and extension of the wrist and grasping motions of the hand are thought to repeatedly compress the median nerve between the tendons and carpal bones, leading to injury to the median nerve. These motions also place a person at risk for the development of tendinitis and the accompanying swelling of the synovial sheath within the carpal tunnel with secondary compression of the median nerve.[9-12]

Analysis of sequential histologic sections of cadaveric wrists has shown evidence of vascular, connective tissue and nerve damage that is greatest in the carpal tunnel and less pronounced proximally and distally.[9] Intraoperative measurement of carpal tunnel pressures in patients with the syndrome compared with controls has shown significantly greater pressures in those with the carpal tunnel syndrome.[10] Evaluating the canal pressures in cadaver forearms has shown that flexing the wrist and loading the flexor tendons can cause pressures of as great as 400 mm of mercury in the space occupied by the median nerve as it passes through the carpal tunnel.[11] These studies supported the biological plausibility of associating the carpal tunnel syndrome with repeated trauma.

Several studies of other occupations have also shown the association of the syndrome with exposure to repetitive motion. Armstrong and Chaffin analyzed the work practices of 18 women with the carpal tunnel syndrome compared with 18 controls. While no differences in hand size were identified between the two groups, there was significantly greater hand force and frequency of pinching motions among those with the syndrome.[13] Cannon and co-workers did a case-control study of 30 subjects in an aircraft engine assembly plant who were identified as having the carpal tunnel syndrome. Three variables were found to be predictive of the development of the carpal tunnel syndrome: using vibrating hand tools, a history of a gynecologic operation and the duration of employment. Persons with the syndrome were significantly more likely to be doing repetitive motion tasks involving the wrist.[4] Falck and Aarnio studied 17 of a total of 20 butchers for evidence of clinical symptoms, signs or nerve conduction velocity abnormalities. Of the 85% who participated, 53% (9) had symptoms and abnormal median nerve conduction velocities consistent with carpal tunnel syndrome.[5] While these studies support the association of the carpal tunnel syndrome with repeated wrist flexion and extension, as well as grasping, they are limited by either the lack of controls or the potential for selection bias.

That 7 of a total of 13 diagnosed cases of the syndrome occurred in a single trade, grocery checking, supports the association of the carpal tunnel syndrome with excessive workplace tasks involving repetitive motion. The cases identified represent more than 50% of the checkers who were evaluated during that period. None of the checkers had a history of rheumatoid arthritis, hypothyroidism, previous wrist fracture or the use of birth control pills. Two of them had had tubal ligations, but none reported a gynecologic operation such as an oophorectomy that might affect hormonal state.

There are several limitations to this thesis. Unlike some clusters of work-related disease where an uncommon disease presents among a small group of workers, the carpal tunnel syndrome is a common illness and grocery checking is a common occupation. For this reason, selection bias may be operating to give the appearance that an excess of the disorder is occurring when it is not. Several factors argue against this cluster being a product of selection bias. The association of the syndrome with repetitive motion is biologically plausible and it has been associated with repetitive motion in several other occupations. Finally, the onset of the symptoms in relation to work—in some, particularly with a change in work process to an electronic scanner—and the excellent response of symptoms and median sensory latencies to removal of the putative cause, repetitive motion, support the work-related nature of the illness.

The identification of this cluster of the carpal tunnel syndrome among grocery checkers is important because this disorder may lead to significant impairment and loss of livelihood and because of the large number of workers at risk. There is a need for more definitive epidemiological studies to explore further the nature and extent of the risk for the syndrome among grocery checkers. If the risk is found to be significant, these studies could be the basis for designing

checkstands that minimize the motions found to be risk factors for causing the carpal tunnel syndrome. As with all occupational diseases, preventing the disorder should remain the primary goal.

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THE CORPORATE PHYSICIAN TODAY

ALTHOUGH THE DISEASES GENERATED by work have been recorded since history's early millenia, relatively few of today's medical practitioners have knowledge of the qualifications or functions of the contemporary occupational physician. Because of legislative mandates, litigious assaults and manufacturing plant misadventures, industry and commerce, more than ever before, have had to seek skilled professional guidance in the preservation of worker health.

In light of the increasing complexity of today's technology in the manufacturing of chemicals, metals and plastics, the fabrication of computers and the use of numerical control equipment, the conduct of biomedical research and the issues involved in genetic engineering, educative and consultative assistance has been needed by industry to avoid job-generated morbidity and mortality.

With the passage of the Occupational Safety and Health Act of 1970, training programs were established and fiscally supported in a number of university-based educational resource centers. Many graduate students have completed curricula in the several disciplines composing the general arena of occupational health. Included among them have been physicians who, after a preparatory clinical year, have undertaken the rigorous programs involved in residency training in occupational medicine. Sequentially, these same physicians, following the two-year program, have met the qualifications for application and passage of the examinations required to be certified as diplomates of the American Board of Preventive Medicine in the specialty of Occupational Medicine.

How do these fully prepared physicians differ from other medical practitioners? Special skills appropriate to the identification, measure and control of the work-site hazards toxic to humankind's many bodily organ systems; the epidemiologic review of employed populations and their comprised responses to contact with work materials; the initiation and continued execution of wellness programs targeted toward the amelioration of factors placing employees at health risk; the mediation of emotional stressors; the familiarization of exposed personnel with the toxicity of contact substances, and the management of departments comprising physicians, nurses and industrial hygienists (occupational environmentalists) represent but some of the expected abilities of a physician who serves as the interpreter to executive managers of the inherent health dangers in their varied workplaces.

The corporate medical director, often a vice-president on the officer or executive ladder, has responsibilities not only for the well-being of the organization's workers, but for the notification and clarification of hazards to the transporters, users and recyclers of the company's products. Further, the medical arm of an institution must guarantee the safety of residents in the community, so that the Bhopal disaster is not replicated at other manufacturing sites. For these sophisticated and knowing actions, as founded on a broad base of clinical and research findings, the occupational physician must be uniquely prepared.

With the ever-enlarging body of toxicologic knowledge, a medical director is expected to share such knowledge with workers, supervisors and executives in a clear and understandable fashion. The transmission of factual data requires communication skills, an insight into behavior—anxiety, apprehension and fear accompany every task involving the potential compromise of health—honesty and a compassion for personnel whose truncated education or experience will prove occupationally limiting. To serve the institution well in these areas, a collateral wisdom is needed in sociology, cross-cultural differences, psychology, business and organizational theory.

Today's executive, particularly a management school graduate, wants nothing less than a highly sophisticated medical practitioner as the counselor in affairs concerning potential jeopardy of human health. Such a knowing physician is mandatory in today's complex world of industry. It is hoped that an understanding of the contemporary demands made of physicians in the corporate world will prove of interest to fellow practitioners who provide medical care to their worker-patients and their families.

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Tracheostomy Tube Failure in Obstructive Sleep Apnea

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In our institutions we routinely do posttracheostomy sleep studies on patients being treated for obstructive sleep apnea. We have identified several patients who failed to show objective evidence of improvement after tracheostomy. From our studies we have found that both mechanical obstruction and concomitant respiratory control dysfunction caused this failure. A unique tracheostomy tube was constructed to treat the subset of patients with internal collapse of the tracheostomy tube.

(Rodman DM, Martin RJ: Tracheostomy tube failure in obstructive sleep apnea. West J Med 1987 Jul; 147:41-43)

Once it has been determined that a patient suffers from obstructive sleep apnea, a treatment plan must be formulated. Treatment options include pharmacologic, mechanical and surgical procedures.[1-5] When feasible, follow-up sleep studies are done after administering treatment in an attempt to document success as measured by improved arterial oxygenation and the absence of apneic periods. Tracheostomy has been found to be very successful and, because of this, a subsequent sleep study is often omitted after a surgical procedure.[6,7] We have found that tracheostomy is not uniformly successful and that a follow-up nocturnal oxygen saturation study or formal sleep study may aid in identifying these patients.

We present three cases wherein tracheostomy failed to prevent nocturnal desaturation and apneic periods. The first is a unique case of internal kinking of the tracheostomy tube resulting in persistent obstructive sleep apnea. The second and third cases illustrate the more widely recognized causes of tracheostomy failure in patients with obstructive sleep apnea: external obstruction of the tracheostomy orifice and concurrent central sleep apnea or respiratory drive dysfunction. A discussion of the approach to diagnosis and treatment of tracheostomy failure follows.

Reports of Cases

Case 1

The patient, a 45-year-old man, presented for evaluation of increasing pedal edema. He had had a 40-kg weight gain to 148 kg (326 lb—280% of ideal body weight) during the year before admission. Subsequently typical symptoms and signs of sleep apnea and right heart failure developed. On physical examination the findings of right heart failure and a short, thick neck confirmed the presence of the obstructive sleep apnea syndrome. Arterial blood gas determinations with the patient breathing room air showed a pH of 7.46, partial carbon dioxide pressure (P_{CO_2}) of 36 torr and partial oxygen pressure (P_{O_2}) of 62 torr (normal for Denver, pH 7.35 to 7.45, P_{CO_2} 34 to 38 torr and P_{O_2} 65 to 75 torr). Pulmonary function studies showed a forced expiratory volume in one second (FEV_1) of 1.3 liters (55% of predicted) and a forced vital capacity (FVC) of 1.75 liters (60% of predicted).

A sleep study was done showing virtually continuous periods of partial and complete obstructive apneas. These were associated with arterial oxygen desaturation to 50%. A regimen of nasal continuous positive airway pressure (CPAP) and supplemental oxygen failed to relieve the apneic periods. A tracheostomy was done.

After the tracheostomy, a sleep study was carried out showing persistent apneic periods associated with arterial oxygen desaturation. A t-piece was used to deliver oxygen, thus eliminating the possibility of obstruction of the tracheostomy orifice, but without benefit. Various lengths and types of plastic endotracheal tubes were used, also without benefit. Using a fiber-optic laryngoscope, the tracheostomy tube was entered. The patient's neck was then actively flexed and extended. When the patient's head was flexed forward, in a position similar to his sleeping position, internal kinking of the tube with complete obstruction was observed.

A noncollapsible endotracheal tube was constructed (Figure 1) and inserted. A follow-up sleep study documented pronounced improvement in nocturnal oxygen saturation with no periods of apnea.

Case 2

The patient, a 37-year-old man, began snoring in his teen years after a weight gain from 73 to 95 kg (161 to 209 lb). His weight then increased to 175 kg (386 lb—310% of ideal body weight). Typical symptoms and signs of sleep apnea developed, with headache, daytime hypersomnolence, restless sleep and hypertension. On laboratory evaluation he had an erythrocytosis, and blood gas determinations with the patient breathing room air showed pH 7.42, P_{CO_2} 34 torr and P_{O_2} 59 torr. Pulmonary function tests showed an FEV_1 of 2.85 liters (77% of predicted) and an FVC of 3.68 liters (80% of predicted).

A polysomnographic study showed 30 to 40 partial and complete obstructive apneic periods per hour. Baseline arterial oxygen saturation was 92%, falling to 50% to 70% during apneic periods. Therapeutic trials of nasal CPAP, supplemental oxygen, protriptyline hydrochloride and weight loss were unsuccessful. A tracheostomy was done.

Subsequent to the tracheostomy, his symptoms persisted.

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

The results of a repeat sleep study were unchanged from baseline. During sleep, the external tracheostomy orifice was observed to be obstructed by the patient's soft tissues. Protecting the orifice with a tracheostomy collar failed to ameliorate the problem. A neck support (Figure 2) was constructed, after which a sleep study showed resolution of the apneic periods. The patient has tolerated the prosthesis well, with total resolution of symptoms.

Case 3

The patient, a 69-year-old man, was admitted for evaluation of mental status changes and hypercapnia. He had long-standing chronic bronchitis and for several years had typical symptoms and signs of sleep apnea. On presentation he was a somnolent, obese man with physical findings of right heart failure. Arterial blood gas determinations with the patient breathing two liters of nasal oxygen showed a pH of 7.28, P_{CO_2} 75 torr and P_{O_2} 48 torr. After vigorous therapy with steroids and bronchodilators, his blood gas values improved to pH 7.39, P_{CO_2} 66 torr and P_{O_2} 55 torr. Pulmonary function tests showed an FVC of 1.63 (38% of predicted) and FEV_1 of 1.21 (42% of predicted). Thyroid function was normal. A sleep study was done showing 75 partial and complete episodes of apnea per hour and 21 episodes of hypopnea per hour—associated with decreased but present respiratory effort. These periods were associated with arterial oxygen saturation as low as 28%. A tracheostomy was done.

A sleep study carried out 14 days after the tracheostomy showed a decreased number of apneas but persistent periods of hypopnea with arterial oxygen desaturation to 80%. Arterial blood gases measured with the patient breathing 35% oxygen showed pH 7.36, P_{CO_2} 74 torr and P_{O_2} 57 torr. A regimen of progesterone, 20 mg taken orally every eight hours, was started. A follow-up sleep study after seven days of therapy showed elimination of the hypopneic periods and maintenance of arterial oxygen saturation at greater than 90%. A follow-up arterial blood gas study with the patient breathing room air was pH 7.42, P_{CO_2} 46 torr and P_{O_2} 61 torr.

Discussion

Clinical Approach to Diagnosis and Treatment

In each of our patients, a posttracheostomy sleep study showed a lack of improvement in nocturnal oxygenation and continued periods of disordered breathing. As these cases show, there are several possible reasons for this failure.

The first is external obstruction of the tracheostomy orifice due to redundant submandibular and neck soft tissue. This diagnosis can often be made by observing the patients during sleep. They will be noted to flex their heads forward, obstructing the orifice. If this is noted, treatment of the disorder can often be effected by protecting the tracheostomy orifice with a tracheostomy collar. If this proves ineffective, a supportive device (Figure 2) can be constructed to maintain the head in a neutral position during sleep.

If these measures prove ineffective, then a second cause, internal obstruction of the tracheostomy tube, should be suspected. This again may be due to redundant neck and submandibular soft tissue. In this case the tracheostomy tube itself kinks or is obstructed at the distal end. In addition to redundant soft tissue, distal obstruction may be due to tracheal stenosis or granuloma formation occurring months to years after a tracheostomy. Internal obstruction can be differentiated from external obstruction by administering oxygen directly with a t-piece while documenting persistent periods of obstructive apnea and arterial desaturation. Direct observation with a fiber-optic laryngoscope is useful to confirm that a properly sized tracheostomy tube is in place and to document the internal obstruction.

Figure 1.—A tracheostomy tube was constructed with a wire coil-reinforced endotracheal tube.

Figure 2.—The photograph shows patient 2 with supportive device in place.

We have found that all commercially available types of plastic tracheostomy tubes are ineffective in these cases. Metal tracheostomy tubes, while likely to be effective, are often not well tolerated by patients. For these reasons, we have constructed a tracheostomy tube using a coiled wire-reinforced type of tube (Figure 1).* The tube length is determined by direct measurement using a fiber-optic laryngoscope. The tube is then fitted with a standard 15-mm adapter and flanges.

If these mechanical measures fail to correct the nocturnal desaturation, then concurrent central sleep apnea or respiratory drive dysfunction should be suspected. It is rare for these disorders to go undiagnosed on a pretracheostomy sleep study. Their importance relative to the obstructive component, however, may be difficult to determine before a tracheostomy.[8] A repeat sleep study will show persistent hypopnea or central apneic periods if these are the cause. Because of the possibility of improvement in central drive after a tracheostomy, this study should be done several weeks after the procedure. Paradoxically, patients with mixed-type apneas (both decreased effort and upper airway obstruction) may, in some cases, show a slight increase in the number of central apneas and hypopneas following tracheostomy.[7] Blood gases done with the patient breathing room air may show resting hypercapnia out of proportion to the degree of lung disease if respiratory drive dysfunction is the cause. This can be confirmed by documenting an appropriate fall in the arterial P_{CO_2} during coached hyperventilation or by formal respiratory drive studies. If these causes are shown, then treatment with either respiratory stimulants or diaphragmatic pacing should be instituted.[3,9,10]

*The authors thank Shirley Phister, RN, for expert advice on constructing tracheostomy tubes.

A final cause of nocturnal arterial oxygen desaturation following tracheostomy should be noted. Exacerbations of ventilation perfusion mismatch due to left ventricular failure and chronic obstructive lung disease may occur at night. In addition, accumulation of airway secretions may worsen at night. The respiratory pattern may be normal or show periodic hypopneas or a Cheyne-Stokes pattern.[11,12] Therapy in these cases should be directed at the underlying problem and may include the use of supplemental oxygen.

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Ethnic Variability in Cholelithiasis—An Autopsy Study

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By reviewing 3,506 autopsy records to determine the prevalence of gallbladder disease among San Francisco county coroner cases for 1981 and 1982, we found an overall prevalence rate of 92.7 per 1,000. After confirming age as a significant risk factor ($P \leq .0001$), the data were age adjusted and then analyzed using a stepwise logistic regression. Women were found to have a twofold to threefold greater prevalence compared with men. Latina women showed a higher prevalence than whites, blacks or Asians. Black women did not have a significantly higher prevalence than the white sample. Actual to ideal weight was also significantly related to the presence of gallbladder disease.

(Arevalo JA, Wollitzer AO, Corporon MB, et al: Ethnic variability in cholelithiasis—An autopsy study. West J Med 1987 Jul; 147:44-47)

Gallstone disease represents a major health problem in the United States today. Approximately 20 million Americans have gallstones and 1 million new cases of gallstones will be diagnosed this year. About 10,000 Americans each year die of gallstone disease and its complications.[1] It is estimated that each year more than a million people are admitted to hospital for cholelithiasis, and, of these, half will be treated surgically.[2] Cholecystectomy has been estimated to be the most common intra-abdominal procedure in general surgery.[3]

In the past decade our understanding of the pathophysiology of cholelithiasis has greatly increased, and a number of risk factors have been identified, the strongest being sex and ethnicity. Early autopsy studies have shown that women have two to three times the prevalence of gallstones compared with men, and whites have twice the prevalence of blacks. Other factors that appear related to the incidence of gallstones include age, obesity, parity, using estrogens and diabetes mellitus.[4-7]

The present study was designed to investigate whether the high prevalence of gallbladder disease among Latina women and the low prevalence among black women compared with white women could be shown in an urban population and to document prevalence rates among Latino men and Asian men and women, about whom little information exists. We used autopsy records to examine the prevalence of gross gallbladder disease by age, sex, body weight and ethnicity.

Methods

Data Collection

The California Government Code and the Health and Safety Code cite 22 circumstances that require reporting a death to a county coroner. Briefly, all deaths of suspected accident, suicide or homicide victims or death surrounding known criminal acts are required to be reported. All solitary deaths or deaths without medical attention within 24 hours are subject to reporting.

In this study, we reviewed the consecutive autopsy reports of all 3,506 persons aged 15 and older on whom the San Francisco County Coroner conducted postmortem examinations in 1981 and 1982. Because of the relative rarity of gallbladder disease in persons 14 years of age and younger,[8] such cases were excluded. Age in years, sex, height in inches and weight in pounds were taken from the face sheet of the reports.

Ethnicity was determined from the face sheet except in the case of Spanish-surnamed subjects listed as white. In these cases, prosector designation ("40-year-old Latino male"), place of birth and name of next of kin were used to establish whether the subject was to be considered Latino or white. Asians with Spanish surnames were assumed to be Filipino. In ambiguous cases, ethnicity was coded as unknown.

Gallbladder disease was defined as present if the prosector noted any of the following in the report: surgical absence of the gallbladder, presence of cholelithiasis or choledocholithiasis and evidence of acute cholecystitis or chronic cholecystitis. The recording of the gallstones by the prosector did not contain a description of stone composition. A gallbladder was considered normal only if the prosector so specified it; otherwise its condition was considered unknown.

Data Analysis

Descriptive statistics regarding the prevalence of gallbladder disease were compiled by ethnicity and sex. In addition, we calculated the ratio of actual to ideal body weight for each subject using the suggested weight standards of the National Research Council Food and Nutrition Board.[9]

Age was adjusted for using the direct method described by Armitage. Analyses of the interaction between variables of

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TABLE 1.—*Demographic Breakdown of Autopsy Cases by San Francisco Coroner, 1981 and 1982 (N=3,506)**

Ethnic Group	Men, Percent	Women, Percent	Percent of Sample	Percent in Community†
White	46	26	72	52
Black	9	4	13	13
Latino	4	2	6	12
Asian	6	2	8	21
Other and undetermined	1	..	1	2
Total	66	34		

*N=Total number of completed autopsies.
†Based on United States Census Data, 1980.[12]

age, sex, ethnicity and actual to ideal weight were examined through the use of a logistic regression model. The methods of Hosmer and Lemeshow and C. C. Brown[10,11] were used to test the goodness-of-fit. Ethnicity was compared as Latino versus non-Latino in the determination of significance.

Results

The Autopsy Sample

The mean age in our sample was 58.7 years, with 53% of the sample older than 60 years. We were able to code ethnicity on 99.8% of the cases. Table 1 shows the breakdown of the sample by ethnicity and sex, comparing these with 1980 census figures for San Francisco County.[12] Whites were overrepresented in our sample (72% sample, 52% census), whereas Asians (8% sample) and Latinos (6% sample) were underrepresented (21% and 12% census). Blacks were accurately represented (13% sample). Men were overrepresented, constituting 66% of the sample.

We compared the prevalence figures for gallbladder disease in the entire sample with those of a smaller sample corrected for sex and ethnic distribution in the population. The results were virtually identical, so we used the entire sample for all subsequent analyses.

Prevalence of Gallbladder Disease

Of the 3,506 subjects 15 years of age or older, we had information on the condition of the gallbladder in 3,173 (91%). Of these, there were 294 cases of gallbladder disease, for a crude prevalence rate of 92.7 per 1,000.

Risk Factors Associated With Gallbladder Disease

The stepwise logistic regression procedure confirmed the relationship between age and sex in both women and men. Ethnicity and ratio of actual to ideal weight were significant only in the female population.

Sex and ethnicity as risk factors. Figure 1 shows the age-adjusted prevalence of gallbladder disease by sex and ethnicity. The prevalence among men was lower than among women ($P \leq .001$). In men, the prevalence ranged from about 6% to 11%, whereas in women prevalence ranged from about 10% to 29%. Latinos had the highest prevalence among men (11.3%), although this was not a statistically significant finding. Latinas, in contrast, had more than twice the prevalence compared with the white subjects (29.3% versus 12.9%). This difference was statistically significant ($P < .05$). Black women showed a slightly higher prevalence compared with the white sample (17.4% versus 12.9%), although this difference was not statistically significant.

Actual to ideal weight as a risk factor by sex and ethnicity. Among the women, the ratio of actual to ideal weight was significantly related to the presence of gallbladder disease ($P \leq .005$). Among men, the difference between subjects with disease and with normal gallbladders is not clinically significant (Figure 2). When Latinas are compared with women of all other ethnic groups, there is a statistically significant difference ($P \leq .01$) between those with normal and diseased gallbladders. Both the Latina and black subjects tended toward obesity in the normal gallbladder group (Figure 3). Latina women with disease had a mean actual-to-ideal-weight ratio that exceeded the standard definition of obesity (20% over ideal weight).

Age as a risk factor by sex and ethnicity. Age at death was significantly related to the presence of gallbladder disease ($P \leq .0001$). The mean age in both men (62.4 disease versus 54.7 normal) and women (71.4 disease versus 62.0 normal) is

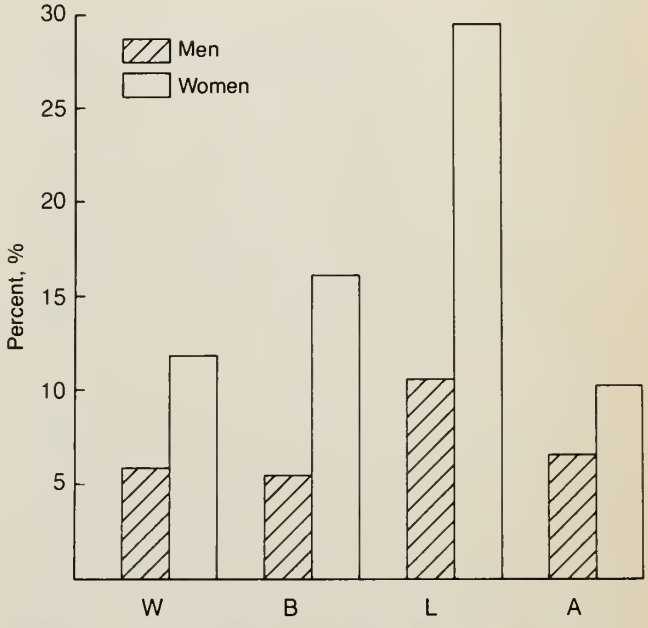

Figure 1.—The graph shows an age-adjusted comparison of an autopsy sample by ethnic group. A = Asian, B = black, L = Latino, W = white

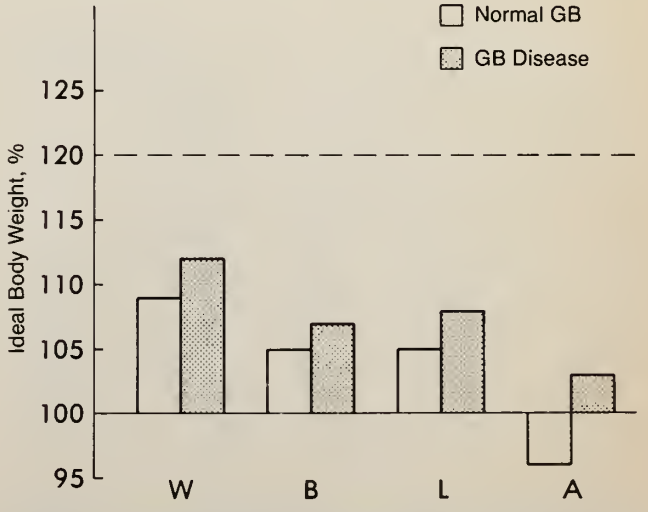

Figure 2.—The graph shows a comparison of percentage of ideal weight of an autopsy sample by ethnic group for men. A = Asian, B = black, GB = gallbladder, L = Latino, W = white

eight to nine years greater in the gallbladder disease category when compared with normals.

As shown in Figure 4, the mean age among the white female subjects with normal gallbladders was about ten years greater than among the Latina, black and Asian female subjects (65 versus 55, 52 and 55, respectively). On the other hand, the mean age of black women with disease was much lower than that of the Latina, white and Asian women with disease (64 versus 73, 75 and 73, respectively).

Among men the mean age of whites, Latinos and Asians with disease was about 15 years older than among the black subjects (64, 64 and 64 versus 49, respectively). The white and Asian men with normal gallbladders were, furthermore, about ten years older at death compared with the Latino and black normal men (56 and 59 years versus 46 and 48, respectively) (Figure 5).

Discussion

Our study confirms previous findings that suggest a higher prevalence of gallstones in the female population. In all ethnic groups except Asians, the prevalence was two to three times higher among women compared with men, even after accounting for the higher average age at death among women.

Our study also confirms previous findings that age is an important factor in the development of gallbladder disease.[5,13-17] Subjects with gallbladder disease were an average of eight to nine years older when they died than subjects with normal gallbladders. Of those who died after 60 years of age, 9.7% of the men and 16.9% of the women had gallbladder disease.

In contrast to some earlier studies, our data do not support the finding that prevalence is lower in the black compared with the white population. A probable explanation for the higher prevalence in the black population in our study is that it is related to an increased life expectancy among blacks now compared with that of the earlier studies, even though it still lags behind that of the white population. We had a relatively larger number of blacks older than 60 years compared with the previous autopsy studies. Our sample included a much larger percentage of black men (28%) and of black women (38%) older than 60 years than did the Cunningham and Hardenbergh (19% men, 13% women)[13] or Lieber (18% men and 22% women)[14] studies.

Lieber used prosector records from Philadelphia and found a 22% prevalence rate among white women, 9% among black women, 10% among white men and 3% among black men.[14] Later, Cunningham and Hardenbergh studied 6,200 autopsies in Alabama and reported an 11% prevalence in white women, 5% in black women, 7% in white men and 2% in black men.[13] Jaffe documented an 18% prevalence rate for white women in Chicago, compared with 10% for black women, 7% for white men and 1% for black men.[15]

Diehl and co-workers in a retrospective study at the Family Practice Clinic at the University of Texas in San Antonio showed that the incidence of confirmed gallbladder disease was 15% among Mexican-American women compared with 9% among white and 4% among black women.[16] Weiss and colleagues used hospital records in Laredo, Texas, to

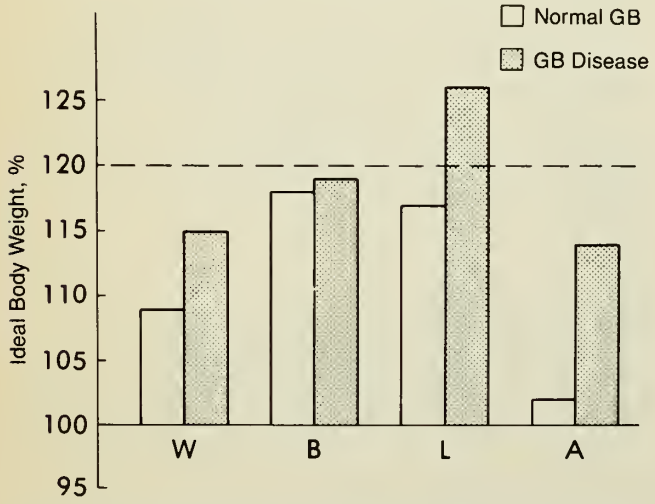

Figure 3.—The graph shows a comparison of the percentage of ideal weight of an autopsy sample by ethnic group for women. A = Asian, B = black, GB = gallbladder, L = Latino, W = white

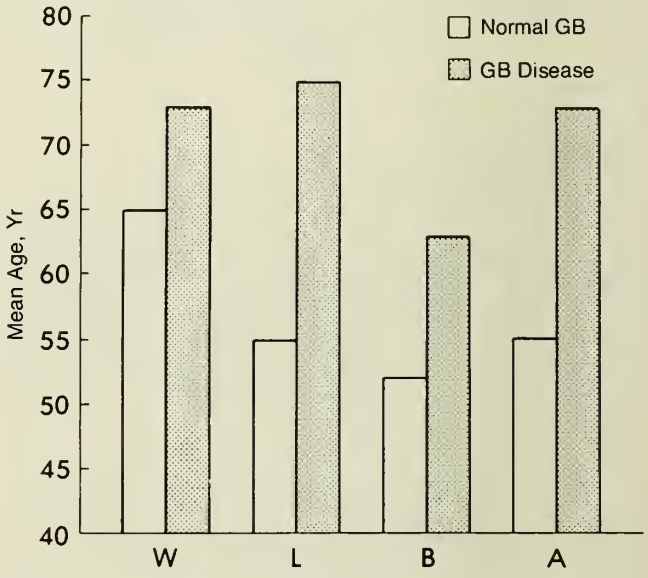

Figure 4.—The graph shows a comparison of mean age at death by ethnic group for women. A = Asian, B = black, GB = gallbladder, L = Latino, W = white

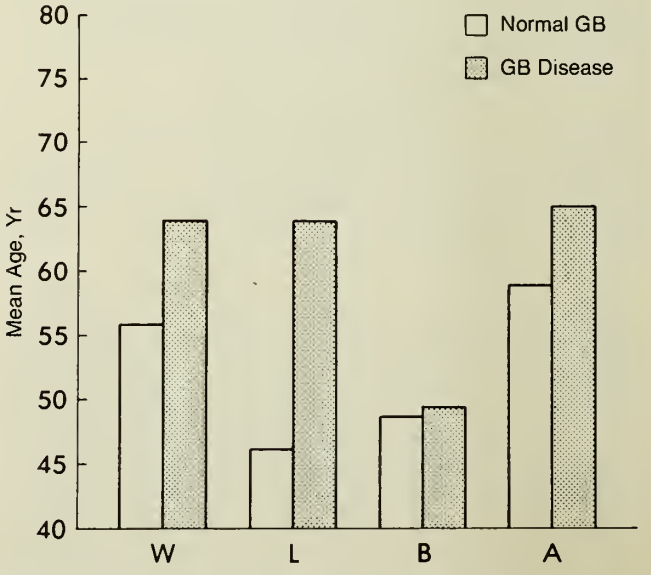

Figure 5.—The graph shows a comparison of mean age at death by ethnic group for men. A = Asian, B = black, GB = gallbladder, L = Latino, W = white

document 33% prevalence of clinically diagnosed gallbladder disease by age 55 among Laredo Mexican-American women.[18] In neither of these studies were men directly compared.

Our finding that more than a quarter of the Latina population had confirmed presence of gallstones or a prior cholecystectomy, twice the prevalence compared with whites, is remarkably similar to the results of Diehl and Weiss and colleagues.[16,18] The prevalence rate for Latino men, which has never before been reported, is similar to the rates in the three other ethnic groups studied and is not significantly different from that of whites. The reason for the discrepancy in the high rate of gallbladder disease in Latina women compared with the Latino men is unclear and suggests that, at least in this population, ethnicity alone is not a uniform factor.

There is strong evidence that gallbladder disease is particularly common among Native-American groups. Comess and associates cited a 32% prevalence of gallbladder disease among women and 6% among men in the Pima Indians using a retrospective chart analysis similar to that used in the Framingham study.[17,19] Sampliner and co-workers, in a similar Pima Indian population, analyzed hospital records combined with prospective cholecystogram results to define a remarkable incidence of 65% in women and 32% in men.[20] Few data exist on the prevalence of gallbladder disease in Asians in the United States. Yamase and McNamara reported a high percentage of admission for gallbladder disease for Chinese patients as opposed to whites in one Hawaiian hospital.[21]

Obesity has been documented to predispose to gallbladder disease, although the exact mechanism is not entirely clear.[4,22] Our overall study population was in general not obese, although men averaged 7% and women averaged 11% above their ideal weights. We found large differences in average weight among our sex and ethnic subgroups that paralleled the prevalence figures for gallbladder disease, suggesting that obesity is a major predictive variable. Black women, both normal and diseased, and normal Latina women had average weights that approached the standard definition of obesity (120% of ideal weight). Latina women with gallbladder disease on the average exceeded this definition of obesity. This apparent association between obesity and ethnicity among women confirms data reported in previous studies and may at least partially explain the relationship between sex, ethnicity and gallbladder disease.

The use of autopsy data carries with it a number of other inherent problems. First, we had no information on several other factors that have also been associated with gallbladder disease including pregnancy,[23] diabetes mellitus,[14,19] estrogen use,[24] diet,[25] surgical procedures,[26] hemolytic anemia, [27,28] cirrhosis and liver disease.[29,30] Second, the coroner's data did not differentiate between cholesterol and pigment gallstones. This difference may be of significance because pigment gallstones are usually associated with particular chronic disease processes such as liver disease, cirrhosis and hemolytic anemias that may be more frequent in this county coroner population. Moreover, bilirubin stones may be more common than cholesterol stones in Asian populations. Third, the discovery at autopsy of evidence of past or present gallbladder disease does not give us any information about whether the disease was clinically significant or the age of disease onset. On the other hand, autopsy data do allow us to look at important clinical information on a large cross-section of the population. Furthermore, because many of the earlier studies in this area were also completed with autopsy information, it has allowed direct comparison of our findings with those of others.[31]

In this study, the determination of ethnicity was based entirely on a subject's surname, prosector designation, place of birth and surname of next of kin. Several cases were excluded because ethnicity could not be determined, but these accounted for only 0.2% of the cases studied. It is possible that some Latinos born in the United States with a non-Spanish surname or an Asian with similar characteristics were miscategorized. It is also unfortunate that the tabulating system did not allow us to further subdefine the Latino and Asian ethnic groups—that is, Mexican-American, Puerto-Rican, Chinese, Vietnamese and so forth. Intraethnic variability and recency of immigration may play an important but unknown role in the potential for the development of this disease.

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Medical Progress

Association of α_1-Antitrypsin Deficiency With Lung and Liver Diseases

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α_1-Protease inhibitor (α_1-Pi) deficiency is associated with emphysema, neonatal hepatitis and cirrhosis. The deficiency associated with emphysema has multiple alleles. Cigarette smoke may influence the onset of emphysema in a twofold manner: by overwhelming the concentration of α_1-Pi by increasing elastase release, and by inactivating the α_1-Pi active site through oxidation. α_1-Pi-associated hepatic disease occurs primarily in children with the allele PiZZ, most of whom are asymptomatic although in a small percentage severe obstructive jaundice and fatal juvenile cirrhosis develop. Pharmacologic intervention and α_1-Pi replacement therapy are being tested against α_1-Pi-associated emphysema.

(Resendes M: Association of α_1-antitrypsin deficiency with lung and liver diseases. West J Med 1987 Jul; 147:48-53)

Since the late 1800s it has been recognized that mammalian serum has the capacity to inhibit the enzymatic activity of various proteases. This activity was later ascribed to the α_1-globulin peak in plasma. In 1963, while studying routine electrophoretic strips, Laurell and Eriksson noted that three of their patients who lacked α_1-globulin peaks had pulmonary emphysema (see Figure 1).[1] This was the first association between decreased protease inhibition and a disease state. Five years later, the absence of this peak was noted again in a patient with cirrhosis. Both this patient and his brother (who also had liver disease) were shown to have low serum trypsin inhibitory capacity because of low levels of α_1-globulins, known as α_1-antitrypsin.[2] Subsequent studies have shown that in patients with severe deficiencies in α_1-antitrypsin, emphysema and hepatic disease appear to develop—and possibly other organ dysfunctions. The question in current α_1-antitrypsin deficiency research is whether or not patients with partial deficiency are at increased risk for the development of certain diseases. Perhaps the most important aspect of this research is in giving insight to the pathogenesis of these diseases.

Biochemical Aspects

α_1-Antitrypsin is composed of a single 394 amino acid polypeptide chain containing four carbohydrate side chains (including galactose, mannose, acetylglucosamine and sialic acid) with an overall molecular weight of 51,000 daltons.[3] In human plasma, α_1-antitrypsin is the major α_1-globulin and on a molar basis is the most abundant protease inhibitor.[4] About 95% of trypsin inhibitory capacity in human serum is due to α_1-antitrypsin.[3] Because α_1-antitrypsin can inhibit a variety of proteases, its current preferred name is α_1-protease inhibitor (α_1-Pi). Enzymes inhibited by α_1-Pi include a polymorphonuclear leukocyte elastase, collagenase, macrophage cathepsin, plasmin, thrombin, factor IX, pancreatic elastase, renin, chymotrypsin, trypsin and a nonspecific protease capable of digesting vascular basement membranes.[5,6] α_1-Pi is found in many bodily fluids including saliva, lymph, perilymph, tears, semen, amniotic fluid, cervical mucus and synovial fluid. It is also found on platelets and megakaryocytes.[7]

The mechanism of action appears to be through attachment to a protease catalytic site of serine enzymes. The reactive site for this inhibitor is a methionyl-seryl bond.[8] Proteolytic digestion of α_1-Pi (with excess elastase) can inactivate α_1-Pi although, in so doing, the α_1-Pi cleavage product complexes with elastase to inhibit it.[9]

In serum, exogenous α_1-Pi has a half-life of about six days. It has been called a "suicide" protein because once it forms a complex with its target proteases, it is cleared by the reticuloendothelial system. It is then excreted by the liver primarily through catabolization; it is recognized as a molecule to be cleared through the galactosyl residues that are exposed as the sialic acid residues are removed.

α_1-Pi is a heat-labile peptide and at a pH slightly less than 5 will be irreversibly inactivated. If, however, α_1-Pi is run through electrophoresis at a pH of about 5.2 (close to its isoelectric point), a microheterogeneity pattern is seen similar to that of hemoglobin.[10]

Despite substantial chemical characterization, the biologic function of α_1-Pi is not completely known. α_1-Pi inhibits proteases in vitro, suggesting that its in vivo function is to protect healthy tissue from proteolytic damage,[4] particularly that caused by protease release from dying cells.[11] As a proteolytic "defense" protein for normal tissues, its levels should increase during periods of physiologic stress, and this has been observed, for instance, with inflammation. The normal plasma concentration of α_1-Pi of 2 to 5 grams per liter (40 to 100 μmol per liter) can increase as much as fourfold over in response to the general stimulus of infection, inflammation and also with estrogens. This increase reflects an increase in synthesis rather than a decrease in excretion.[9] α_1-Pi deficiency states, in contrast, show a smaller rise in α_1-Pi plasma concentration with stress—at most a doubling of the basal levels.

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in 1 second
Pi = protease inhibitor

Analysis of α_1-Pi Activity

Historically, the measurement of α_1-Pi was based on the trypsin activity and inhibition. Synthetic substrates like *N*-benzoyl-DL-arginine-*p*-nitroanilide or benzoyl arginine ethyl ester were placed with a known amount of trypsin and then analyzed spectrophotometrically, providing a measure of the enzyme's activity. While trypsin standardization was a problem in the past because of commercial variation, pooled samples from reference laboratories have enhanced standardization.

Radioimmunodiffusion is another common screening procedure. α_1-Pi is placed in the central well of an agar gel plate containing its corresponding antibody. The α_1-Pi then diffuses through the agar, precipitating as it reacts with the antibody. The resulting precipitin line is a function of the concentration of antigen. This test normally correlates well with the spectrophotometric test. The exception is the case of a nonfunctioning inhibitor, where antigen is present without activity.

The development of crossed immunoelectrophoresis, however, allows the accurate detection of variants and, therefore, is superior to the two previously mentioned tests. This test is a two-stage process. The first stage consists of acid starch gel electrophoresis with banding separation of α_1-Pi. The second stage consists of transferring the starch gel strip to an agarose gel containing its corresponding antibody and then doing a second electrophoresis at right angles to the direction of the first. This produces a series of precipitation peaks that accurately correspond to the α_1-Pi variants.

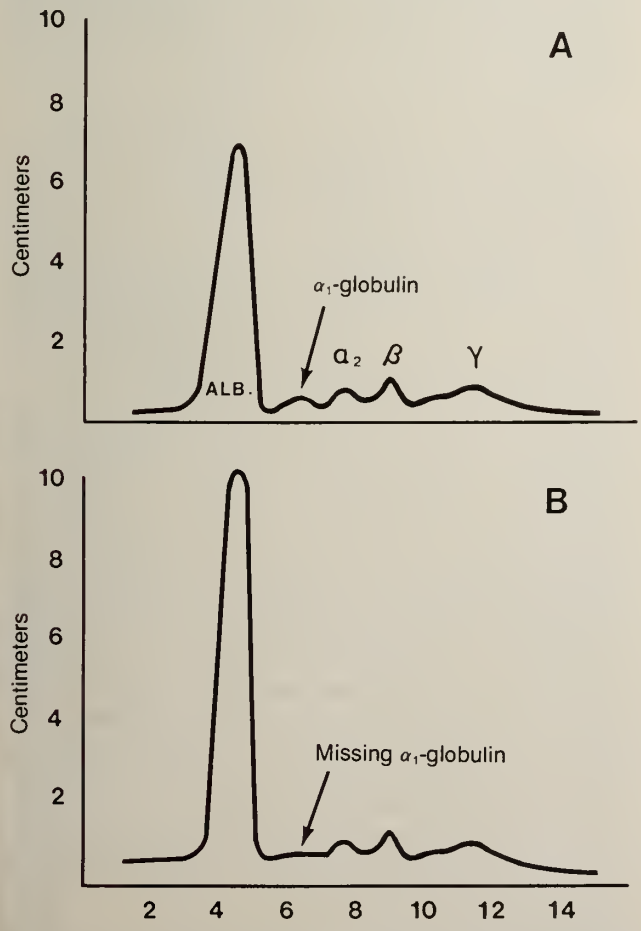

Figure 1.—The graphs show electrophoretic assays of human serum: Note that normal serum (**A**) shows an α_1-globulin peak that is notably absent in the patient suffering a deficiency of enzyme inhibitor (**B**). ALB. = albumin

Isoelectric focusing in polyacrylamide gels provides an improved technique over crossed immunoelectrophoresis. It is less time-consuming because it requires only one gel run and is sensitive enough to detect subtypes of some of the alleles.[3] The expensive equipment required remains a drawback to most private biologic laboratories.

Most recently specific oligonucleotide-hybridization analysis has allowed the identification of PiMZ heterozygotes as well as SS and ZZ homozygotes by direct analysis of the mutation site on the α_1-Pi allele.[12] With this method α_1-Pi deficiency can be detected prenatally and postnatally.

Genetics and Epidemiology

Familial factors have been recognized since 1862 when it was noted that younger patients with emphysema seemed to have a strong family history of this disease. A basis for this familial predilection was Laurell and Eriksson's finding of a link between α_1-Pi deficiency and emphysema in the early 1960s.[1] It has since been recognized that α_1-Pi deficiency is associated not only with lung disease (emphysema), but also with liver disease (notably neonatal hepatitis and cirrhosis). The lung disease is more common in adults, while the liver disease predominates in infants and children. Other less frequent diseases reported with severe deficiency include hepatic tumors, recurrent pancreatitis, membranous glomerulopathy and severe panniculitis,[4] although data supporting these relationships remain controversial.

The genetics of this protein suggest the presence of two independent alleles at a single locus with autosomal codominant inheritance. To date, 31 different alleles have been shown. Each person, therefore, is born with two genes capable of producing α_1-Pi, with each gene possibly encoding a separate variant of α_1-Pi. The variants are classified by the protease inhibitor (Pi) nomenclature in terms of their electrophoretic mobility at pH 4.9. For example, PiSS is homozygous for an anodal variant (with low mobility), whereas PiMM, which is the normal, is encoded by the M allele (having medium mobility).[13] Because of the existence of a silent or null gene (labelled Pi^- or Pi_{null}), patients who phenotypically seem to be homozygotes are designated with only single letters—PiZ—unless the patient is proved by genotyping to be homozygous, at which point PiZZ would be used.

The significance of these alleles lies in the varying plasma levels they produce and the disease states being associated with the decreased plasma levels. PiM is the commonest genotype and is considered to produce normal levels. PiZ homozygotes and Pi^- are most often connected with disease and with severely decreased plasma levels (Table 1). In clinical practice, disease seems to be limited to patients with serum plasma levels less than 40% of normal.

As stated above, α_1-Pi from patients with the deficiency is electrophoretically distinct from that in normal persons, but it has not been distinguished immunologically nor functionally from normal persons—that is, milligram for milligram, Z-type protein can inhibit trypsin or elastase as well as M-type

protein.[4] Although deficient forms have been shown to be structurally different from normal, serum clearance is not significantly changed, with resultant similar half-lives.

The two significant alleles besides the normal M are the S and Z. The PiZ deficiency variant reflects the substitution of lysine for glutamic acid at amino acid number 264, while the PiS variant reflects glutamic acid replaced by valine at amino acid number 342.[14] Single point mutations occur in both instances. The Z allele occurs with one haplotype.[15] Differences in the carbohydrate content also exist, in particular the amount of sialic acid, although the exact difference has not been elucidated. The change in amino acid may be what produces the molecule's inability to attach a normal complement of sialic acid.

The actual mechanism by which the structural difference between Z-type protein and the M type decreases plasma levels of α_1-Pi is unknown. One hypothesis is based on the presence of an amorphous material accumulating within most hepatocytes of PiZZ persons. Light-microscopic analysis of hepatocytes has shown that it takes up the periodic acid-Schiff stain (as does glycogen) but is diastase-resistant, in contrast to glycogen accumulations, and is immunologically similar to α_1-Pi,[16] although it lacks sialic acid. Electron microscopy of these hepatocytes shows that the earliest and greatest amount of the material exists in the smooth endoplasmic reticulum[17] as a precursor of α_1-Pi that generally remains unsecreted. It appears that the abnormal α_1-Pi molecule is incompletely processed, with only a small portion being sialylated and excreted into the circulation. This hypothesis, however, does not account for other allelic variants that do not show the accumulation of precursor substance in the liver.[12]

The liver is the primary source of plasma α_1-Pi. Proof of this was found when persons undergoing liver transplantation acquired the phenotype of the donor liver—with patients with the α_1-Pi deficiency subsequently having normal α_1-Pi levels.[18]

As with other proteins showing slight allelic variances, such as hemoglobin, the frequencies of different Pi types vary from population to population. In the United States where considerable gene mixing has occurred, PiM has a reported allele frequency of 0.87. The PiMZ phenotype is found in 2.2% to 3.0% of whites and PiMS in 6.5% to 8.0%. Non-PiM alleles are rare in black Africans. In Europe the prevalence of PiS is higher in Iberians, as is that of PiZ in Scandinavians (see Table 2).[19] A subpopulation of the Northern-Southern European division of alleles was found by a genetic study in Italy. Genetic typing done on 3,751 people from Italian towns showed a progressive decrease in Z alleles in the Italian population extending from north to south.[20] Finally, just as the sickle variant of hemoglobin appears to have survival advantages—that is, heterozygotes have increased resistance to the malaria parasite—accounting for its persistence in the population, there may be an evolutionary reason for deficiency genes such as PiZ. One possibility is increased fertility in heterozygous women because decreased inhibition of protease could decrease cervical mucus viscosity, providing a more favorable medium for the passage of sperm.[21]

TABLE 1.—*Effect of Genotypic Inheritance on Plasma Levels of α_1-Protease Inhibitor**

Genotype	Plasma Levels, Percent
MM	100.0
ZZ	15.0
SS	60.0
SZ	37.5
MZ	57.5
MS	80.0
$PiM^{(Malton)}$	15.0
Pi⁻	0.0

*From Laurell and Jeppsson.[10]

TABLE 2.—*Allelic Variances in European Populations**

Population	Total Number of Subjects	Alleles, Percent M	S	Z	F
Belgium	549	93.4	5.4	0.73	0.36
Spain	954	87.5	11.3	0.80	0.10
France					
Languedoc	1,520	91.0	7.9	0.59	0.13
Lyon	1,653	90.2	7.1	1.4	0.36
Bretagne	280	84.6	7.5	2.3	0.36
Holland	672	94.5	2.5	1.8	0.22
Norway	2,830	94.6	2.3	1.6	1.3
Great Britain	4,042	93.7	4.5	0.94	0.35

*From Braxel et al.[19]

Pathogenesis of Emphysema

The protease-inhibitor imbalance theory, based on the work by Gross and Pfitzer and colleagues, helps to explain the role of cigarettes in the pathogenesis of emphysema.[22] To be comprehensive, this theory must address several important questions:

- Which proteolytic enzyme is involved?
- Does it have an endogenous or an exogenous source?
- Which proteolytic inhibitor is involved?
- Finally, how does cigarette smoke influence the balance among these preceding factors?

Gross and co-workers placed papain in the tracheas of hamsters, leading to digestion of the alveolar walls. Within several weeks, the pathologic and physiologic characteristics of pulmonary emphysema developed in the animals.[22] α_1-Pi given intratracheally can prevent the appearance of emphysematous lesions in hamsters administered papain.[23]

Papain is not found in animals, but other proteases capable of producing emphysematous lesions in animal lungs were extracted from purulent sputum and from the granules of polymorphonuclear leukocytes. One protease is leukocyte elastase, which cleaves elastin (at aliphatic amino acids), a major structural protein of lung alveoli.[6] (The elastin content does not seem to be reduced in emphysema, but its amino acid composition is altered, resulting in alteration of lung elasticity.) Elastases are normally released in vivo by damaged or dead polymorphonuclear leukocytes and macrophages. Measuring the associated rate constants of α_1-Pi with various proteases gives, in decreasing order of magnitude, leukocyte elastase, chymotrypsin, cathepsin G, anionic trypsin, cationic trypsin, plasmin and thrombin.[4] Therefore, for patients deficient in α_1-Pi, an endogenous protease (elastase) exists that can damage the lung architecture and normally can be well inhibited by α_1-Pi, while in states of deficiency this protease may be unchecked.

Most patients with emphysema, however, do not have a deficiency of α_1-Pi, and therefore the third and fourth questions become important. Cigarette smoke affects the protease

TABLE 3.—*Subjects With Type SZ**

Cases	Subjects, number	Mean Age, yr	Dyspnea %	Dyspnea Age at Onset, yr	% Predicted Forced Expiratory Volume in 1 s	% Predicted Vital Capacity	% Predicted DL_{CO}	X-ray Evidence of Emphysema, %
Index								
Smokers	12	54	83	48	51	77	55	75
Nonsmokers	2	51	0	..	65	75	80	0
Nonindex†								
Smokers	8	48	13	48	101	99	82	13
Nonsmokers	3	38	0	..	125	123	102	0

DL_{CO}=carbon monoxide diffusing capacity of the lung

*From Tobin and Hutchison.[27]
†Nonindex cases were relatives of the index-case patients with the SZ phenotype.

inhibitor balance. An increased number of polymorphonuclear leukocytes and macrophages is found in the lungs of smokers compared with nonsmokers (using bronchial lavage). Smoke condensate causes polymorphonuclear leukocytes and macrophages to release their elastase in vitro. Further, elastase release from both macrophages and neutrophils is also greatly enhanced by cigarette smoke,[24] resulting in an increased protease load with cigarette smoking. Most emphysematous patients seem to have adequate levels of α_1-Pi to counter this increased load. The α_1-Pi found at the site of action, however—that is the alveoli—may be oxidized by cigarette smoke (cigarette smoke may modify a methionine residue at the active center of α_1-Pi), thereby inactivating the molecule. Oxidation, if it occurs, should increase the negative charge of the protein, thereby increasing its electrophoretic properties in plain agarose, and this has been shown to occur.[25] Cigarette smoke thus increases the amount of elastase and inactivates α_1-Pi.

Why does emphysema not develop in all cigarette smokers? Although many explanations have been offered, this question remains unanswered. Current views include a varying amount of cigarettes smoked, the role of intermediate levels of α_1-Pi and the role of other inhibitors such as α_2-macroglobulin, the other major serum protease inhibitor.

α_1-Pi-Associated Emphysema

Of the many alleles found for the α_1-Pi protein, the PiZZ and PiSZ phenotypes are most clearly associated with emphysema. In the United States, 30,000 persons homozygous for α_1-Pi deficiency are at risk for emphysema.[5]

Eriksson studied a group of 33 in-hospital patients with α_1-Pi deficiency.[26] Of these, 23 had clear evidence of pulmonary emphysema; 60% of the patients were younger than 40 years, and 90% were younger than 50. Fagerhol, doing electrophoresis on specimens from 13,000 patients, identified 70 persons having PiZZ phenotypes; 44 of these patients had emphysema.[21] Of interest, serum levels of α_1-Pi were not lower in subjects with emphysema than in those without.[2] This suggested that the expression of the genetic defect in clinical illness may depend on the interaction with other genes or perhaps exposure to some environmental agent.

These two initial reports were followed by a British Thoracic Association study (1975) to accurately determine the prevalence and severity of pulmonary disease and the relative influence of genetic and environmental factors on the natural history of the disorder. In this study, patients who had a PiZ or PiSZ pattern were classified as index cases, and nonindex cases were relatives who also showed PiZ or PiSZ patterns. The results from that study, summarized in Tables 3 and 4,[27] show that deficient patients have a higher incidence of emphysema than the normal population. Smokers appear to acquire a significantly increased risk, although there were smoking subjects with normal spirometric values and gas transfer, suggesting that other factors are important in causing lung disease.

Most clinical features of emphysema in the α_1-Pi-deficient patients are no different from those found in other emphysematous patients. These patients show reductions in forced expiratory volume in one second (FEV_1) and the ratio of the FEV_1 to vital capacity, specific conductance and an increase in total lung capacity, functional residual capacity and residual volumes. Radioactive xenon studies show a more severe reduction in ventilation in the bases as compared with the apices.[28] Differences do exist between Pi-nondeficient and deficient patients who have emphysema. The age of onset approaches 40 years for the Pi-deficient, smoking patients, as opposed to 60 years for nondeficient smoking patients. Men have an increased risk of emphysema developing, even when the smoking risk is accounted for. This is an interesting finding because equal-sex involvement would be expected with codominant allelic inheritance.

A genetic study supports previous data on the anatomic location of α_1-Pi emphysema: 97% of type Z homozygotes with emphysema had some disease in one or both lower zones, and in 62% the upper zones were unaffected.[29] This corresponds to the preponderance of basal emphysema at autopsy in patients with α_1-Pi deficiency. Conflicting results regarding the risk of PiMZ and PiMS phenotypes continue to occur. Most studies have found no difference in the prevalence of respiratory symptoms or spirometric abnormalities. Larsson and co-workers studied 43 PiMZ men with PiM-matched controls and found significantly higher abnormalities of elastic recoil, residual volume and closing capacity in PiMZ smokers as opposed to PiM smokers.[30] Therefore, although there may be subtle differences between PiMZ and PiM subjects, they have not been striking.

α_1-Pi-Associated Liver Disease

Unlike α_1-Pi-associated emphysema where a connection between low plasma levels and various alleles is seen, α_1-Pi-associated hepatic disease occurs primarily in PiZZ persons, but not in PiSS phenotypes. As mentioned earlier, hepatocytes of ZZ-phenotype persons have large intracellular globules in the smooth endoplasmic reticulum. This material reacts with fluorescent-labeled α_1-Pi antibody and is considered to be the Z variant protein but with immature carbohydrate

TABLE 4.—*Subjects With Type Z**

Cases	Subjects, number	Mean Age, yr	Dyspnea %	Dyspnea Age at Onset, yr	% Predicted Forced Expiratory Volume in 1 s	% Predicted Vital Capacity	% Predicted DL_{CO}	X-ray Evidence of Emphysema, %	Dead %	Dead Years
Index										
Smokers	108	49	92	39	31	70	42	93	19	52
Nonsmokers	18	57	78	48	51	75	70	74	17	60
Nonindex†										
Smokers	24	48	58	44	63	86	63	73	0	..
Nonsmokers	16	54	44	43	75	85	84	56	0	..

DL_{CO}=carbon monoxide diffusing capacity of the lung

*From Tobin and Hutchison.[27]
†Nonindex cases were relatives of the index-case patients who had Z phenotype.

side chains. Extracellular deposits of a similar material have been noted, but this material does not appear to combine with fluorescent-labeled antibody.[31]

About 80% to 90% of PiZ subjects have no clinical evidence of liver disease in infancy, although 50% have abnormalities on liver function tests by 4 years of age.[32] Severe obstructive jaundice develops in 7%, with a smaller proportion having progression to fatal juvenile cirrhosis. The affected children show signs of hepatomegaly during their first year of life along with an obstructive jaundice pattern that generally resolves by age 6 months, only to be followed by a gradual but relentless and severe portal hypertension.[2] Affected and nonaffected PiZ persons do not have a significant difference in their plasma α_1-Pi levels. Why such a large variation exists in severity is unknown. The similarity of the liver disease in most families supports the hypothesis that a second genetic factor may be necessary. Recently 67 PiZ children were prospectively studied, starting with infancy.[32] Of the children in whom liver disease developed, 78% had a similarly affected younger sibling even though they had heterozygous PiMZ parents. Heterozygotes normally incur a 25% chance of having a child with a particular homozygous phenotype, yet this study showed a significantly higher incidence in certain families. The data reinforce the second genetic factor hypothesis,[32] whereas there may also be a hormonal factor because males are predominantly affected.[33]

Breast-feeding may offer some protection against severe liver disease and early death in persons with α_1-Pi deficiency. This has been postulated as follows: In neonates there is an enhanced uptake of exogenous macromolecules from the intestinal lumen to the systemic circulation. Perhaps luminal enzymes can also be taken into the systemic circulation and then to the liver, causing inflammation and eventually fibrosis. Human milk has protease inhibitors, including α_1-Pi. Hence, α_1-Pi can form neutralizing complexes with luminal enzymes.[34] This hypothesis has been somewhat supported by evidence that portasystemic shunts in α_1-Pi-deficient infants are protective against severe liver disease.[35]

Finally, in earlier experimental work it was shown that peripheral blood lymphocytes from children with α_1-Pi deficiency and liver disease were cytotoxic in vitro to isolated rabbit hepatocytes. Most recently, cytotoxicity with T and non-T cells against autologous hepatocytes in vitro in children with PiZZ phenotype has been shown to increase with age. It has not been shown to play an important role in the pathogenesis of the initial liver injury associated with α_1-Pi deficiency but may have a role in perpetuating the liver cell damage.[36]

Liver disease due to α_1-Pi deficiency occurring in adults independent of childhood disease is rare. A large Scandinavian autopsy study comprising 700 patients with the deficiency showed amorphous liver globules in 26 (4%), with fibrous and nodular regeneration occurring only in 6.[37] Other studies have linked the deficiency to hepatocellular carcinoma. Whether these cases actually are independent of childhood disease or a continuation of childhood disease will probably not be known until a large prospective study of PiZ infants through adulthood is done.

Scattered reports exist of the association of α_1-Pi with other diseases (pancreatitis, rheumatoid arthritis, panniculitis, membranous glomerulopathy), but most have had equivocal results. Most prominent has been α_1-associated membranous glomerulopathy. It is thought that leakage of Z protein from dying liver cells acts as an antigen for immune complex deposition on basement membranes.

Therapy

Because there has been no specific mechanism theory for α_1-Pi liver disease, no treatment modality has been postulated. For α_1-Pi deficiency-associated emphysema, however, there can be therapeutic effects. First and foremost for PiZ, PiSZ and perhaps PiMZ persons is avoiding pulmonary irritants. In particular these patients should be encouraged to avoid cigarette smoking or working in industries with dust and smoke and to seek early treatment for respiratory tract infections.

Danazol, a testosterone analogue, was recently tested in α_1-deficient patients. It produced a 50% increase in α_1-Pi levels in most of the patients.[38] Another pharmacologic intervention has been the development of synthetic protease inhibitors such as chlormethyl ketones. These drugs are still only in the experimental stages, but they have been useful against experimentally induced emphysema.[39]

A promising therapeutic approach has been the replacement of α_1-Pi through plasma fractions and now by genetically engineered α_1-Pi.[40] Gadek and Crystal in 1982 tested α_1-Pi replacement therapy on a group of deficient patients. By intravenous infusions they maintained plasma levels of 35% normal—an arbitrary level where minimal necessary coverage is found. After four weeks of therapy, bronchoscopy showed 60% of normal α_1-Pi activity and no elastase activity, whereas pretherapy bronchoscopy had shown an absence of functional α_1-Pi and active elastase activity.[41] A major drawback of α_1-Pi replacement therapy is the five-day half-life of α_1-Pi, necessitating frequent replacement.

Conclusion

A great deal of interest has surrounded the study of α_1-Pi deficiency since its link to emphysema in 1963. A pathogenetic model for emphysema has resulted in possible therapeutic modalities now being tested for α_1-Pi-deficient patients with emphysema. The ultimate goal is the development of therapy for nondeficient emphysematous patients. α_1-Pi-associated liver disease occurs in PiZZ persons and predominantly in infancy and childhood. The mechanism of disease is still unclear.

Many unanswered questions still remain. Among these, the following are foremost: do heterozygotes have an increased risk for emphysema developing? and do other organ systems also suffer from α_1-Pi-associated liver processes? The evidence is still unclear in these areas.

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Specialty Conference

Cardiac Ischemia. Part II—Reperfusion and Treatment

Moderator
GLENN A. LANGER, MD

Discussants
GERALD D. BUCKBERG, MD, *and* JAN H. TILLISCH, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

(Langer GA, Buckberg GD, Tillisch JH: Cardiac ischemia. Part II—Reperfusion and treatment [Specialty Conference]. West J Med 1987 Jul; 147:54-61)

GLENN A. LANGER, MD: In the previous issue we reviewed the physiologic and metabolic responses to cardiac ischemia. It was noted that there were immediate (within seconds to minutes) alterations in potassium flux and loss of contractile function after the onset of ischemia. These responses are implicated in the electrical dysfunction that results in sudden death and in the mechanical dysfunction that produces early pump failure. Following this acute phase there is a period of one to six hours during which metabolic dysfunction develops, which can be accurately monitored with the use of positron emission tomography (PET). These studies indicate the possibility of a major dissociation of blood supply and metabolic activity in the ischemic zone. The preservation of metabolic activity, as defined by PET, can be used as an objective indication in the determination of benefits to be expected by reperfusion.

In this issue the focus is on treatment with emphasis on surgical reperfusion (Dr Gerald Buckberg) and thrombolytic therapy and percutaneous transluminal angioplasty (PTCA) (Dr Jan Tillisch).

Myocardial Response to Reperfusion

GERALD D. BUCKBERG, MD:* The immediate recovery of regional contractility does not follow normal blood reperfusion after a duration of coronary occlusion as short as 15 minutes,[1] and segmental shortening may not return for as long as a month after two hours of temporary ischemia, if the working heart is reperfused with unmodified blood.[2,3] Coronary occlusion of six hours' duration is thought to produce such extensive transmural necrosis[4,5] that clinical muscle salvage cannot be expected even a year after reperfusion. Consequently, there is limited enthusiasm for either medical (streptokinase or angioplasty or both) or surgical—that is, coronary artery grafting—revascularization in patients who have had acute occlusion for six hours.

Our experimental studies have extended the period of regional ischemia to this six-hour interval. Our results, first, show the remarkable structural and functional integrity of transmural myocardial tissue after six hours of ischemia; second, document the extensive "reperfusion injury" produced by normal blood reperfusion with the heart in a beating working state after only four hours of ischemia, and third, show that modification of reperfusion damage, muscle salvage and immediate functional recovery is possible after six hours of ischemia by careful *control of the conditions and composition of reperfusion.*[6]

These experimental studies form the basis for our current clinical approach to treating acute myocardial infarction surgically. We shall present our preliminary surgical results and propose a new potential strategy whereby regional blood cardioplegic reperfusion on total bypass without thoracotomy—that is, in the catheterization laboratory—can be accomplished.

Experimental Studies in Animals

In experimental studies on anesthetized dogs whose chests have been opened, the proximal left anterior descending coronary artery was occluded with the heart in a working state to produce an area of risk of about 30%, and regional contractility was assessed by ultrasonic crystals.[6] All dogs underwent cannulation of the femoral artery and right atrium by way of the femoral vein; left ventricular venting was accomplished by the transaortic route (Figure 1) to allow reperfusion on total vented bypass in dogs undergoing controlled reperfusion. These cannulae were connected to a pump oxygenator circuit, and a catheter was placed into the distal left anterior descending coronary artery for regional cardioplegic reperfusion only in those dogs who received blood cardioplegic reperfusion.

Experimental groups differed in duration of ischemia and method of reperfusion:

- *Ischemia without reperfusion.* Seven dogs underwent six hours of acute coronary artery occlusion without reperfusion and transmural biopsy specimens were taken for ultra-

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Part II of a two-part conference. Part I was published in the June 1987 issue.

This study was supported in part by National Institutes of Health grants RO1 HL28539 (Dr Langer), 1R 23 HL27846 (Dr Weiss), HL29845, HL33177 (Dr Schelbert), HL16292 (Dr Buckberg); United States Department of Energy grant DE-AC03-76-SF00012 (Dr Schelbert); Investigative Group Award (Dr Schelbert); Grant-in-Aid from the American Heart Association, Greater Los Angeles Affiliate, and the Laubisch Endowment (Dr Weiss).

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
CoQ_{10} = coenzyme Q_{10}
IV = intravenously
PET = positron emission tomography
PTCA = percutaneous transluminal coronary angioplasty
TPA = tissue plasminogen activator
TTC = triphenyltetrazolium chloride

structural and mitochondrial functional analyses after prolonged ischemia.

• *Normal blood reperfusion in working hearts.* Nine dogs underwent two hours of acute coronary artery occlusion and seven dogs underwent four hours of acute occlusion followed by reperfusion with normal blood at systemic pressure (removal of occluding clamp) in working hearts to simulate angioplasty in a catheterization laboratory without the use of bypass.

• *Blood cardioplegic reperfusion during total vented bypass.* In 20 dogs, the left anterior descending coronary artery was occluded for two hours (5 dogs), four hours (8 dogs) and six hours (7 dogs), respectively. All hearts received regional blood cardioplegic reperfusion on total vented bypass. The conditions of reperfusion and composition of the reperfusion were controlled in the following manner: The conditions of reperfusion, which was modified, included (1) total heart decompression by vented bypass to prevent wall tension from developing in the damaged heart during reperfusion, thereby increasing its oxygen demands[7]; (2) gentle reperfusion pressure—that is, 50 mm of mercury—to limit postischemic edema produced by sudden reperfusion[8]; (3) regional cardioplegia to keep energy demands as low as possible during temporarily controlled reperfusion[8]; (4) normothermia to optimize the rate of cellular repair,[9] and (5) prolonged reperfusion duration—that is, 20 minutes—to maximize excess oxygen uptake relative to demands and avoid premature imposition of high-energy demands.[10] Total bypass was continued for 30 minutes after regional reperfusion and then stopped to allow observation for one additional hour with the heart in the working state.

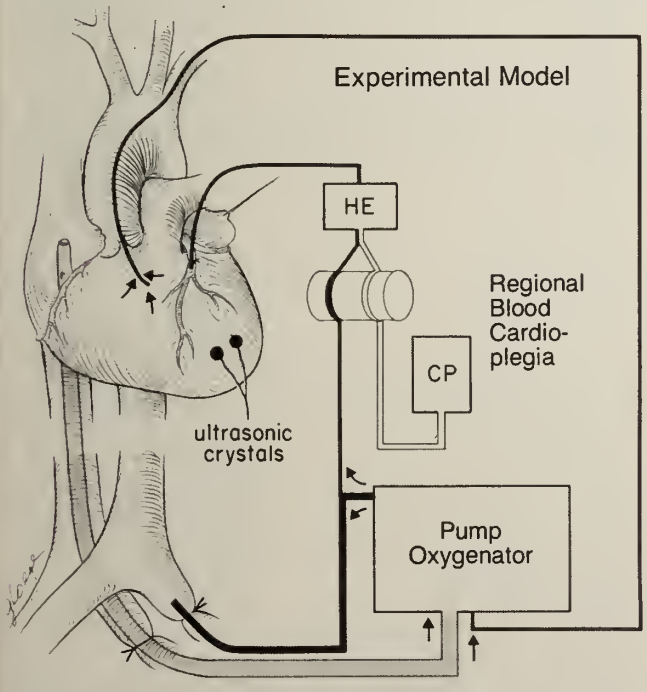

Figure 1.—Experimental model showing peripheral cannulation technique used to achieve total vented bypass without requiring direct right atrial, aortic or left ventricular penetration. Regional contractility was determined by ultrasonic crystals, and regional cardioplegic reperfusion delivered into the coronary artery directly (this can be achieved by a coronary balloon passed fluoroscopically; see text for description). CP = cardioplegic delivery system, HE = heat exchange

TABLE 1.—*Cardioplegic Solution*

Principle	*Constituent*	*Final Concentration*
Provide oxygen	Blood	Hematocrit 20% to 30%
Maintain arrest	Potassium chloride	12 to 16 mEq/liter
Buffer acidosis	Tromethamine	pH 7.5 to 7.6
Avoid edema	Glucose	>400 to 450 mosm
Restore substrate	Glucose	>400 mg per dl
	Aspartate	13 mmol/liter
	Glutamate	13 mmol/liter
Scavenger O_2 radical	Coenzyme Q_{10}	80 μg/ml
Limit calcium entry	Cardioplegic delivery	150 to 250 μmol Ca^{++}
	Diltiazem	300 μg/kg body weight

The reperfusion composition was modified to permit (1) oxygenation with blood, providing substrate (O_2) to generate energy to repair cellular processes[11]; (2) cardioplegia (hyperkalemia) to keep the heart from resuming electromechanical activity and raising O_2 demand[9]; (3) replenishment of amino acid precursors or Krebs' cycle intermediates (that is, glutamate, aspartate) needed to ensure more effective oxidative metabolism to produce energy for cell repair and subsequent mechanical function[12]; (4) limiting calcium influx by reperfusate hypocalcemia (150 to 250 μmol) with citrate-phosphate-dextrose to reduce calcium load, and adding a calcium channel blocking drug (that is, diltiazem) (which could continue to retard calcium cell entry after normocalcemic reperfusion is started)[13]; (5) reversal of acidosis with a buffer to provide an optimal intracellular milieu for effective resumption of metabolic function[14]; (6) hyperosmolarity—that is, using glucose—to minimize postischemic edema and permit cell volume regulation to occur more gradually when normothermic blood flow is restored[15]; (7) membrane stabilization with the use of coenzyme Q_{10} (CoQ_{10}) to avoid damage to the phospholipid bilayer[16,17] and glucocorticoids to limit lysozymal disruption[18]; (8) counteracting oxygen free radicals with oxygen free-radical scavenger—that is, CoQ_{10}—to limit the cytotoxic effects of these compounds, and (9) hyperglycemia to enhance the osmotic effects and perhaps initiate compartmental anaerobic energy production at the onset of reperfusion.[19] These reperfusate principles were accomplished with the agents shown in Table 1—which defines the regional reperfusate used in these studies—but may also be accomplished by other, untested agents (that is, different buffers, oxygen radical scavengers, calcium channel blocking and cardioplegic drugs) that produce these desired effects.

Ischemia for six hours without reperfusion produced only mild structural alterations. Myofibrils were intact, mitochondria showed integrity of the inner and outer membranes and only mild clarification of the matrix. At least 200 mitochondria were examined in each muscle layer in each heart by the low protein denaturation technique,[20] and the average mitochondrial grades ranged from 1.2 in epicardial muscle to 1.9 in endocardial muscle (grade 6 is complete disruption) (Figure 2). This ultrastructural integrity was accompanied by

substantial retention of mitochondrial respiratory function; the adenosine triphosphate (ATP) production rate (stage 3 respiration × adenosine diphosphate/0) was maintained at 64% of control levels (589 versus 925 nmol ATP per grams protein per minute) after six hours of regional ischemia.

Dyskinesia (systolic bulging) persisted throughout the ischemic interval in all experiments. Reperfusion with normal blood with the heart in the beating, working state failed to restore regional systolic shortening after two or four hours of ischemia ($-35\% \pm 6\%$ and $-13\% \pm 4\%$ systolic shortening) measured after the first hour of observation after revascularization. In contrast, immediate recovery of systolic shortening occurred in each of 13 hearts reperfused with substrate-enriched blood cardioplegia on total vented bypass after two and four hours of ischemia ($52 \pm 2\%$ and $40 \pm 7\%$) and in six of seven hearts ($21 \pm 6\%$ systolic shortening) undergoing control reperfusion after six hours of coronary artery occlusion (Figure 3).

Acute coronary artery occlusion produced profound transmural ischemia, reducing flow (radioactive microspheres) to less than 5% of control levels. Reperfusion with normal blood with the heart in the beating, working state after only two hours of ischemia restored transmural flow to only 47% of control levels. In contrast, all hearts reperfused after six hours of ischemia with blood cardioplegia on total vented bypass had pronounced transmural hyperemia (Figure 4).

Histochemical muscle damage (triphenyltetrazolium chloride [TTC] nonstaining) was least severe (12% area of nonstaining versus area at risk) after two hours of ischemia followed by controlled conditions and composition of reperfusate and most severe (73% area of nonstaining versus area at risk, $P < .05$) following normal blood reperfusion after four hours of regional ischemia. More extensive nonstaining followed controlled reperfusion in nonbypassed hearts after four hours of ischemia than after controlled reperfusion following six hours of regional ischemia (73% versus 55%, $P < .05$).

Uncontrolled reperfusion (normal blood in working hearts) after four hours of ischemia produced moderately severe transmural architectural disruption, with the most severe damage (grades 3.7 and 3.4) in endocardial and midmyocardial muscle; there was breakdown of mitochondrial cristae, with filling of the mitochondrial space with amorphous vesicles and intensely stained material. In contrast, the average grade for mitochondrial change after blood cardioplegia reperfusion on total vented bypass was comparable to that occurring with ischemia alone (1.2 and 1.9) where inner and outer mitochondrial membranes were intact and myofibrils were unaltered.

These experimental studies show that immediate partial recovery of regional contractile function is possible after as long as six hours of acute coronary artery occlusion, provided that the conditions of reperfusion and composition of reperfusate are controlled carefully. Such control results in higher postischemic flows and in superior ultrastructure when compared with normal blood reperfusion of working hearts after shorter ischemic intervals (two to four hours).

These data provide experimental confirmation of the inability of "successful" reperfusion with streptokinase or angioplasty, or both, to avoid infarction or restore early con-

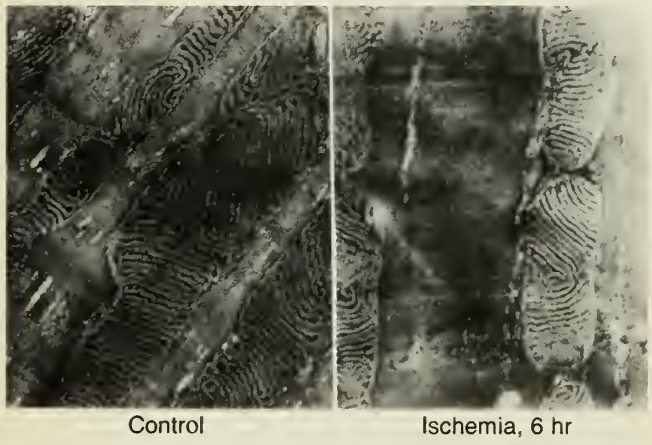

Figure 2.—The mitochondrial ultrastructure, prepared by the low denaturation embedding technique, shows a relatively normal appearance of mitochondria after 6 hours of ischemia (right panel) compared with control (left panel).

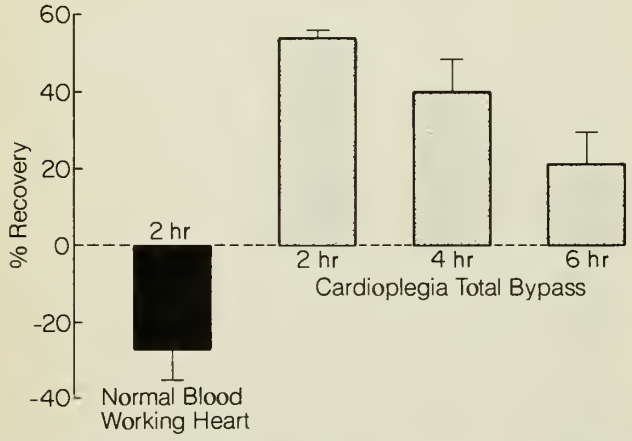

Figure 3.—Segmental shortening after reperfusion, expressed as percentage of recovery of systolic shortening, is compared with control after normal blood reperfusion in working heart (solid bar) and substrate-enriched blood cardioplegic reperfusion on total vented bypass (stippled bars). Note failure to recover systolic shortening after uncontrolled reperfusion at 2 hours (solid bar) and immediate recovery of systolic shortening after 2, 4 and 6 hours of ischemia after controlled reperfusion.

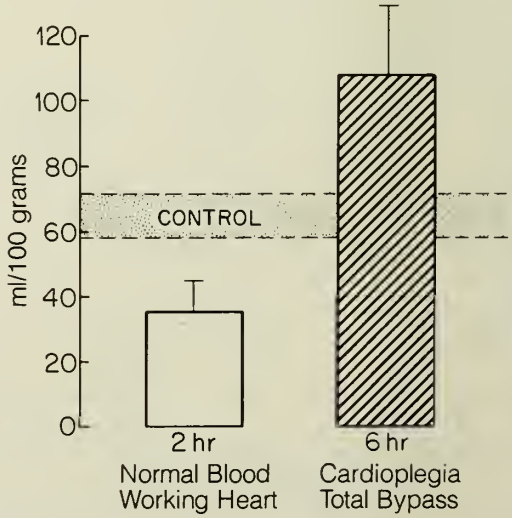

Figure 4.—Left ventricular transmural blood flow (microspheres) is shown after reperfusion with normal blood in working heart (open bar) and substrate-enriched blood cardioplegic solution on total bypass (hatched bar). Control values are shown in stippled bar. Note the low reflow with uncontrolled reperfusion after 2 hours of ischemia and hyperemic flows after 6 hours of ischemia and controlled reperfusion. Units given represent the mean ± standard error.

TABLE 2.—*Global and Regional Contractility*

Cardiac Indices	*Medical Treatment*	*Surgical Treatment*
Global ejection fraction, %	41±2*	47±2*
Regional recovery		
Wall-motion score†	2.5±0.5*	1.3±0.2*‡
Points <2.0	2 of 21 (10%)	12 of 12 (100%)

*Values are mean ± standard error.
†Wall-motion grade: grade 0=normal, grade 1=mild to moderate hypokinesis, grade 2=severe hypokinesis, grade 3=akinesis, grade 4=dyskinesis.
‡$P<.05$.

TABLE 3.—*Control During Reperfusion*

Approach	*Surgical Treatment*	*Medical Treatment*
Arterial inflow	Aorta	Femoral artery
Venous return	Right atrium	Right atrium (via femoral vein)
Ventricular vent	Left ventricle (direct)	Left ventricle (transaortic)
Regional reperfusion	Coronary artery bypass grafting	Coronary catheter

tractile function to regional segments revascularized in the catheterization laboratory.[21-23]

Preliminary Clinical Studies

The principles of reperfusion control emerging from these experimental studies were applied by us in a preliminary series of patients with acute evolving myocardial infarction. We compared the results after surgical control of the conditions of reperfusion and composition of the reperfusate with those achieved by "successful" streptokinase or angioplasty or both, where no attempt was made to exert reperfusate control except to restore blood flow per se to the ischemic segment.

A total of 33 consecutive patients with acute coronary artery occlusion underwent either medical or surgical revascularization. Medical reperfusion was with normal blood in 21 patients in the catheterization laboratory (that is, streptokinase therapy, $N=11$; angioplasty, $N=10$) after 4.4 ± 0.5 hours of acute coronary artery occlusion. Surgical reperfusion was with substrate-enriched (glutamate plus aspartate) blood cardioplegia during coronary artery grafting after naturally occurring occlusion in 12 patients revascularized 8.8 ± 6 hours (range 7.4 to 13.5 hours) after occlusion.[21]

Medical revascularization produced cardiogenic shock (stroke work index <20 grams • m per m^2, pulmonary artery wedge pressure >20 mm of mercury) in 7 of 21 previously hemodynamically stable patients—5 with single-vessel disease—whereas surgical revascularization reversed cardiogenic shock in 6 of 12 patients with preoperative hemodynamic instability due to coronary occlusion. Surgical results were superior in incidence of infarction as recorded by electrocardiogram (57% versus 100%, $P<.05$), severe ventricular tachyarrhythmias (0% versus 43%, $P<.05$), recovery of global ejection fraction (47% versus 41%), recovery of significant regional contractility (100% versus 9%, $P<.05$) and duration of hospital stay (8.8 versus 11 days, $P<.05$), despite a delay of surgical treatment for as long as 12 hours. No patient died (Table 2).

These preliminary clinical results are directly comparable with those achieved experimentally and may lead to the conclusion that selected patients with acute coronary artery occlusion should be treated surgically. Control of the conditions and composition of reperfusion may, however, be achieved medically without thoracotomy (Table 3). The right atrium can be decompressed by way of the femoral vein, arterial influx can be delivered through the femoral artery and left ventricular decompression can be achieved by using a catheter passed transaortically from a peripheral artery, while the regional cardioplegic reperfusate can be administered through a reperfusion catheter advanced through the clot and stenosis as occurs with angioplasty done emergently.

This proposed future approach to patients with acute coronary artery occlusion is shown in Figures 5 and 6. The process of infarction can be arrested by placing a patient on total

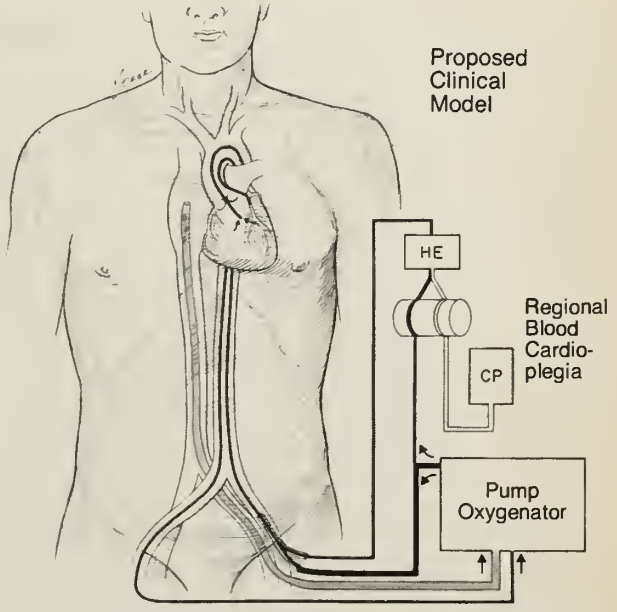

Figure 5.—Proposed experimental model of total vented bypass and regional cardioplegic reperfusion without thoracotomy. Note that the venous return catheter is advanced from the femoral vein to the right atrium, that arterial inflow is through the femoral artery, that left ventricular decompression is achieved by means of a transaortic catheter from the femoral artery and that the reperfusate catheter is passed into the coronary artery by way of the coronary ostia from the femoral artery. CP = cardioplegic delivery system, HE = heat exchanger

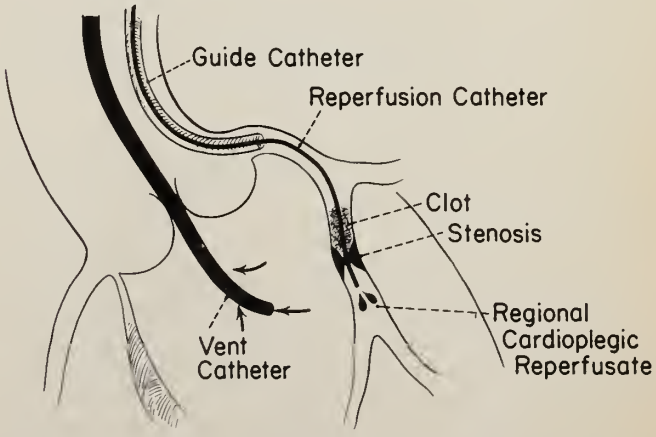

Figure 6.—A close-up version is shown of a proposed technique to decompress the left ventricle via a ventricular vent catheter passed across the aortic valve and a regional cardioplegic catheter passed through a coronary guide catheter, through clot and across the stenotic region into a distal coronary vascular bed (see text for description).

vented bypass in the catheterization laboratory so that an angiogram can be safely carried out and the decision made whether to do controlled regional reperfusion followed by angioplasty (single-vessel disease) or to transport the patient to the operating room on total vented bypass for surgical revascularization (multivessel disease or occluded arteries, or both, that cannot be penetrated by a guidewire).

We interpret the findings of these experimental and clinical studies to indicate that muscle salvage and restoration of early contractile function is possible in myocardium that is ischemic for six or more hours, if there is rigid control of the reperfusate conditions and composition.

Current Approaches in the Treatment of Ischemia

JAN H. TILLISCH, MD:* After many decades of therapeutic focus on the consequences of ischemic injury—arrhythmias, pump failure or mechanical lesions, such as mitral regurgitation, aneurysm or septal defects—in the past decade there has been a shift in the focus toward ameliorating the ischemic injury itself, first by attempting to reduce myocardial oxygen demands and, more recently, by pharmacologically or mechanically restoring perfusion during the evolution of an ischemic injury.

The development of clinical techniques of reperfusion during acute myocardial infarction has made necessary the careful examination of the complex interplay of factors that result in ischemic injury. The duration of ischemia is not the sole determinant of the degree of myocardial injury. The severity of the ischemia (as determined by the presence or absence of collateral flow or by spontaneous early partial reperfusion), the myocardial oxygen demands during the ischemic period and, more important, at the time of reperfusion, the preocclusive metabolic state of the myocardium, the nature of the reperfusate and the hydrodynamics of the actual reperfusion process all may have a significant determinative effect on the degree of myocardial salvage achieved by reperfusion.

We have witnessed during the past five years a flood of clinical and experimental studies showing the technical ability to achieve reperfusion in patients with acute infarction with safety and with a success rate varying between 30% and 100%, depending on the techniques chosen and the patient population studied. The metabolic and functional state of the reperfused myocardial region and the functional and survival characteristics of the patient population are now being addressed in various investigative studies.

Ischemic Injury

A brief review of the consequences of ischemia has been presented in the previous sections (see Part I in the June 1987 issue of THE WESTERN JOURNAL OF MEDICINE, volume 146, pp 713-723).

The temporal sequence of these processes depends on the severity of the ischemia and the metabolic state of the myocardium, as determined largely by the relation between oxygen supply and demand before and during the ischemic interval and at the time of reperfusion.

The optimal current and future therapy for acute ischemic injury must be considered in light of these events. Three general approaches to acute ischemic injury may be considered: first, the more "traditional" approach of attempted pharmacologic reduction in myocardial oxygen demands and enhancement of supply, coupled with aggressive treatment of secondary complications of myocardial infarction (arrhythmia, pump failure) but without attempts at reperfusion; second, attempted reperfusion using thrombolytic agents, particularly streptokinase or tissue plasminogen activator, and third, "mechanical" reperfusion using percutaneous transluminal angioplasty or coronary artery bypass grafting.

Therapy Without Reperfusion

The first mode of therapy is clearly not a static one. Recent studies have suggested that the aggressive use of nitroglycerin given intravenously (IV) in the early stages of acute myocardial infarction reduces postinfarction morbidity.[24] Controversy remains about the initial use of β-blockade in patients with evolving myocardial infarction.[25] Metabolic enhancement with glucose-insulin-potassium infusions seems to be beneficial.[26] The impact, however, of newer pharmacologic means of manipulating myocardial metabolic demands has been difficult to discern, hampered to some extent by the lack of sensitivity of the diagnostic methods used to judge that impact.

Thrombolytic Therapy

Thrombolytic reperfusion has been achieved by the intracoronary administration of streptokinase in about 60% to 80%[22,27] of patients with occluded infarct-related arteries. In these two large randomized studies, the mortality results were discrepant; in the study reported by Rentrop and associates,[22] no significant difference in mortality rates was observed, while in the western Washington trial, a slightly improved survival was noted in the treatment group at one year, but only after statistical adjustment for nonmatching variables in the two groups.[27] As with previous uncontrolled trials, those patients in whom reperfusion was achieved had improved mortality rates, not surprisingly showing that thrombolysis had apparent benefit but that the overall success in a large patient group was limited by the actual success in achieving reperfusion. Because of the need for cardiac catheterization to use this form of therapy, with the attendant delay in application and the logistic difficulties of having catheterization facilities on demand, intracoronary thrombolysis seems to have only a limited application, given the marginal effects observed on mortality results and the lack of effect on ventricular function.[23,27]

Intravenous administration of thrombolytic agents has the obvious appeal of greater speed and ease of administration, with the concomitant drawback, particularly in the case of streptokinase, of an increased systemic thrombolytic state with consequent increased risk of bleeding complications. The reports of nonrandomized trials have suggested again that successful thrombolysis was associated with an improvement in survival both of myocardium at risk and of patients. Documented successful reperfusion, however, was achieved in only 35%[28] in one randomized trial, although higher rates of successful thrombolysis have been reported.[29]

Despite the rather low success rate of the use of IV streptokinase, several studies have shown a lower mortality rate with its use as compared with conventional therapy.[30,31] Factors that may influence those results will be discussed subsequently. Nonetheless, a more consistently effective thrombolytic agent has been sought, and initial trials with tissue plasminogen activator (TPA), derived from recombinant

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DNA technology, are promising. TPA does not induce a systemic thrombolytic state, a theoretic advantage in terms of hemorrhagic complication. The risk of hemorrhage, however, appears to be due to subsequent heparin therapy in most instances, rather than the dose or type of thrombolytic agent. A study comparing IV streptokinase with IV TPA found that 60% achieved reperfusion with TPA as against 35% with streptokinase. Despite this large difference in successful thrombolysis, the hospital mortality rate was not significantly different. The previously shown benefits of successful thrombolysis (as against the benefits accruing to the applied therapy as a whole) suggest that an improved incidence of successful reperfusion is associated with improved myocardial salvage and therefore mortality in the treatment group. The correlation, however, of improved myocardial salvage and improved patient mortality figures has not as yet been conclusively shown with intravenous thrombolytic agents.

Several factors influence the success of thrombolytic reperfusion in myocardial salvage; other factors may influence the effect on patient mortality rates.

The time to reperfusion is obviously a critical factor. Attempted reperfusion after more than 1½ to 2 hours of chest pain in patients with evolving "transmural" infarctions has been associated with little or no effect on regional myocardial function judged by wall-motion studies within one to two weeks of therapy.[32,33] This was found despite comparable success in reperfusion in "early" and "late" treatment groups. Indeed, no study has suggested that reperfusion success itself is influenced by the time of treatment relative to the onset of symptoms. It is the degree of myocardial salvage that seems influenced. Nonetheless, one cannot definitively state from present data that beneficial effects of thrombolytic reperfusion accrue only to those treated early. Subgroup analysis of the reported studies has not been done in such a way as to determine whether enhancing global myocardial blood flow by reperfusion may affect long-term morbidity without necessarily affecting myocardial salvage in the region of the infarction. Findings of the western Washington intracoronary streptokinase trial, where mortality was marginally improved in the treated group without a discernible effect on ventricular function, may be interpreted as supporting the hypothesis of improved survival without "salvage" of infarcting tissue.[23,27] Moreover, analysis of ventricular function in this trial was done at a mean of eight weeks after acute infarction, a sufficient time period to permit return of function of "stunned" but viable myocardium. Determination of regional or global ventricular function at shorter intervals (3 to 14 days in most published thrombolytic trials) may fail to show recovery of function of reperfused myocardium, which at a later date will show improvement in contractile performance, particularly in those patients treated beyond one to two hours of ischemia.

The intensity of ischemia may be an even more important influence on ventricular function and ultimate patient survival than the duration. Three components of this factor may be operative. First, the degree of residual flow through a partially occluded artery, or the degree of spontaneous early reperfusion—that is, before treatment—has been seen only in studies where coronary angiography was done before administration of the thrombolytic agent. The presence of an incompletely occluded artery before therapy (or in control groups) is associated with greater short-term improvement in ventricular function.[22,34] The second component affecting the intensity of ischemia is the presence of collateral flow at the time of pretreatment angiography. Several studies have shown that the improvement in ventricular function after successful reperfusion occurs largely in patients who had angiographically demonstrable collateral flow to the infarct vessel distribution.[35,36] The presence of collateral, residual or early spontaneous reperfused flow seems to have a major effect on the degree of ventricular salvage achieved by thrombolysis, despite being insufficient to avoid infarction altogether. A third component of the ischemic state is the degree of residual coronary luminal narrowing after thrombolysis. Several studies indicate more successful return of contractility in the region of infarct when the residual stenosis was modest[37] or when percutaneous transluminal coronary angioplasty (PTCA) was done early after successful thrombolysis.[38] In addition to the possible beneficial effects of increased blood flow through a minimally obstructed artery on myocardial recovery, the incidence of postthrombolytic reocclusion was lower in those patients with less residual stenosis.[37]

Another factor that may influence the extent of myocardial salvage consequent to reperfusion is the mechanical loading condition of the ventricle at the time of reperfusion. Although often difficult to assess clinically, experimental studies by Buckberg (see previous section) and by Laschinger and associates[39] show the importance of reduced myocardial oxygen requirements through reduction of mechanical work during reperfusion. Whether pharmacologic manipulation of hemodynamics using aggressive coronary and systemic vasodilatation, calcium channel blocking agents or β-blockade have particularly beneficial effects at the time of reperfusion is as yet unexplored but theoretically attractive.

Percutaneous Transluminal Angioplasty

Percutaneous transluminal coronary angioplasty as a mode of primary reperfusion during the evolution of acute infarction has advantages over thrombolytic therapy but clearly counterweighing disadvantages, principally related to the delay in initiating therapy.

The published success rate for reperfusion with PTCA is comparable to the intracoronary administration of thrombolytic agents.[40] The concern noted earlier about the deleterious effects of the residual stenosis is of course obviated by PTCA. Evidence from several studies suggests enhanced recovery of ventricular function with PTCA compared with that with thrombolysis alone.[41,42] The delay inherent in angioplasty, however, although of only modest statistical significance in a large study, may be of major individual significance in a patient with a large but partially collateralized anterior infarction. Again, one must weigh the risk of delay with PTCA as against the risk of failure to reperfuse with IV streptokinase or TPA.

The combination of PTCA with the intracoronary administration of streptokinase or TPA does not seem to enhance successful reperfusion, nor does it diminish the delay in therapy associated with the use of an angiographic technique. The initial use of IV thrombolytic agents (after placing an intraarterial sheath) and then the subsequent use of PTCA seem to offer several advantages: therapy is begun early, ineffective reperfusion may be addressed at cardiac catherization with either additional intracoronary thrombolysis or with PTCA and residual stenosis can be directly dealt with at the time. The disadvantages are that the safety of urgent coronary artery bypass grafting should PTCA result in vascular trauma or reocclusion is compromised by the thrombolytic state; the

logistic concerns regarding the necessity for 24-hour availability of catheterization laboratory remain, and a post-thrombolytic, late-catheterization procedure to determine the degree of vessel patency means a patient would require two coronary angiograms, with the additional expense and risk. If these objections are met with evidence of improved long-term survival, morbidity and ventricular function, then this form of therapy may be an appropriate choice.

Coronary Artery Bypass Grafting

DeWood and colleagues have repeatedly shown that there is a low mortality rate when coronary artery bypass grafting is done within the first six hours of infarction.[43] Although uncontrolled, these studies are compelling if not totally convincing. The delay in reperfusion with immediate coronary artery bypass grafting is substantially greater than with other forms of reperfusion. Logistic and as-yet-undetermined cost considerations aside, the ability to achieve adequate and complete revascularization must be weighed against the loss of possibly salvageable myocardium with this delay. Data discussed previously by Dr Buckberg, however, show that the experimental treatment of ischemic injury is best done when "the conditions and composition" of the reperfusate can be controlled. The period of time during which substantial myocardial salvage can be expected is prolonged substantially by confining initial metabolic efforts after reperfusion to the cellular tasks of membrane maintenance, calcium sequestration, volume regulation and replenishment of metabolic intermediates, high-energy phosphate precursors and stores before requiring contractile work to be done.

The clinical dilemma is determining when the time is past for unmodified and uncontrolled reperfusion. When, in an ischemic injury, does the benefit of a rapidly administered but only partially successful reperfusion technique become less than that provided by modified controlled reperfusion with the attendant delay in application? Moreover, will the logistic concerns and associated co-morbidity of immediate coronary artery bypass grafting be small enough to permit the widespread application of this technique? These critical questions remain to be answered.

Combining PTCA with modification of reperfusion as previously presented has exciting potential for shortening the delay and lessening the morbidity of surgical intervention implicit in selecting immediate coronary artery bypass grafting as therapy, but retains some of the advantages of more effective myocardial salvage, as shown experimentally with coronary artery bypass grafting and controlled reperfusion. This form of therapy awaits further development and validation of its effectiveness.

Current Clinical Choices

At this time, hard clinical data sufficient to determine a clinical course in a patient with acute myocardial infarction are not yet available. Clinical experience, however, coupled with current understanding of the pathophysiology of ischemic injury, permits some guidelines to be developed, with the usual caveats that individual patients require individual approaches and that continued reevaluation of results is required in areas where proof does not yet exist.

Patients who present with acute myocardial infarction and symptoms of a duration of one to two hours or less are best treated with intravenous thrombolytic therapy. Exceptions would of course be those with major hemorrhagic risk or advanced age. The presence of prior myocardial infarction, severe hemodynamic compromise or extension of an acute infarction into other vascular distributions would be situations wherein myocardial salvage may not entirely depend on thrombolysis of a single vessel but rather on the cascade of increased demand on adjacent myocardium with a compromised blood supply. In such cases, the best approach seems to be immediate coronary artery bypass grafting with modified reperfusion of the infarcted vessel and revascularization of other arteries.

In patients who present with an apparent duration of ischemia of between two and four hours, the ability to preserve substantial myocardium seems to be limited largely to those with incomplete occlusion or a collateralized infarct region. The delay associated with demonstration of that state by angiography and proceeding to use either PTCA or thrombolysis with PTCA to follow may therefore have relatively little consequence in terms of myocardial salvage. The greater reperfusion success rate with PTCA, or the intracoronary use of thrombolytic agents, and the opportunity at catheterization to discover a need for multiple lesion revascularization by coronary artery bypass grafting or PTCA might lead one to select coronary angiography as the first step in managing a patient with ischemic injury of two to four hours' duration. If IV tissue plasminogen activator proves to be as successful as PTCA or intracoronary thrombolysis (about 70%), then this would seem to be the preferred initial choice, until such time that nonsurgical controlled reperfusion might become a reality.

It is in this group of patients with ischemia of sufficient duration to militate against myocardial salvage with any but modified reperfusion that there is the greatest confusion as to appropriate therapy. Clearly, diagnostic methods are needed to attempt to differentiate patients in whom sufficient residual flow in the infarct region persists to mandate an early attempt at noninvasive thrombolysis. A short delay in therapy attendant to applying some diagnostic method of differentiating the potentially salvageable from irreversibly injured myocardium would be a reasonable price to pay, if it permits more appropriate application of therapy.

Patients who present with evidence of ischemia for longer than four to six hours will, in general, derive no benefit from immediate thrombolytic techniques. The maximum interval with modified direct reperfusion is as yet unknown. Clearly some patients with chest pain of more than four to six hours will still have substantial myocardium at risk but salvageable. The absence of electrocardiographic Q waves, the continued presence of substantial ST-segment elevation and the presence of hypokinesis or dyskinesis as against akinesis on echocardiography may be "soft" indicators of continued viability. Again, diagnostic methods of determining tissue viability need to be validated.

With any of these techniques, concurrent therapy with IV nitroglycerin, aggressive treatment of congestive heart failure, rigorous control of hypertension and treatment of tachycardia are supplemental and important. Continued investigation into the benefits of pharmacologic agents that may enhance anaerobic metabolism, diminish transmembrane calcium flux, prevent generation of oxygen-free radicals and diminish myocardial membrane injury must be particularly tested in the reperfusion model and subsequently in that clinical setting.

What was once conceived of as an irreversible insult—the

cessation of flow to contracting myocardium—has been shown after short intervals to be partially and potentially reversible. The temporal limits of reversibility in cases of acute ischemic injury have not as yet been clearly defined.

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Editorial Comment

Treatment of Acute Myocardial Ischemia

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The report on myocardial ischemia from the UCLA Department of Medicine (elsewhere in this issue) includes a selective discussion of the mechanisms involved in ischemic injury and emphasizes a series of procedures under investigation for the evaluation, diagnosis and treatment of acute ischemia and evolving myocardial infarction. This is an area of great current interest because of the development of interventions designed to prevent cell death in acute infarction. These include lysis of thrombi in coronary arteries with streptokinase or tissue plasminogen activator, thrombolysis with angioplasty, emergency bypass operations and a new experimental procedure called total vented bypass and regional reperfusion without thoracotomy. This commentary is aimed at providing background information on some of the concepts presented, with emphasis on the biology of ischemia and infarction as it applies to the treatment of acute ischemia in both experimental animals and humans.

Serious efforts to develop therapy for acute myocardial infarction began in the early 1970s with Braunwald and Maroko's popularization of the idea that jeopardized, potentially salvageable myocardium existed for several hours in the left ventricle of dogs and humans with acute myocardial ischemia.[1] It was known from earlier studies that the myocardium of dogs anesthetized for open-chest experiments would tolerate episodes of ischemia of as long as 15 to 18 minutes without necrosis developing. Proof of survival rested on the observation that cell death did not develop in the damaged tissue if it was reperfused with arterial blood. The living myocytes damaged by a brief episode of ischemia were termed *reversibly injured.* After longer periods of ischemia, many of the damaged myocytes died even though the tissue was reperfused and the ischemic state eliminated.[2] These myocytes were defined as *irreversibly injured.* The structural manifestations of lethal injury in ischemic myocytes successfully reperfused with arterial blood have been designated *contraction-band necrosis*, a phenomenon which develops essentially instantaneously in a number of conditions including ischemia and reperfusion (see Ganote for background).[3] These early studies established clearly that not all myocytes in ischemic myocardium die simultaneously.[4] The rate at which cell death occurred in acute regional ischemia in terms of its potential response to treatment was defined by Reimer and Jennings, who showed that necrosis progressed transmurally as a function of the duration of ischemia.[5] The inner layer of the left ventricle dies first; myocytes in the middle and outer layers die sometime later, or not at all. These data formed the basis of numerous studies designed to test whether various drugs would prevent cell death in acute ischemic injury (see Hearse and Yellon for reviews of the topic).[6]

The results of most of these studies of various drug therapies were not convincing because of a variety of problems with the data, including the fact that the initial methods used to estimate infarct size, such as analysis of ST-segment changes or enzyme release into the plasma or enzyme depletion from the area of injury and so forth, proved to be too imprecise and irreproducible. In addition, virtually all early workers failed to recognize that acute myocardial infarcts in animals could vary widely in size under control conditions, and they did not control for the factors that led to the variation. Initially, most papers reported beneficial effects of therapies, including the use of agents as widely diverse as β-blockers, glucose-potassium-insulin, nitroglycerine and steroids. Each agent was reported to reduce some measure of damage resulting from ligation of a coronary artery. In fact, about 80 agents have been reported to reduce infarct size. Few or none of these are used in humans. The scientific world seems to recognize that most of them do not work or do not work sufficiently well to be useful.[6] On the other hand, throughout this period it was clear that cell death resulted from the reduction in arterial flow to the affected myocardium and that cell death could be prevented after varying but brief intervals of ischemia if the arterial flow was restored successfully.

A better understanding of the biology of evolving myocardial infarction occurred in the mid-1970's and developed chiefly because of the development and application of the microsphere technique to the measurement of arterial flow in discrete segments of myocardium.[7] Measurement of arterial flow in ischemic segments by microspheres established the critical role that arterial collateral flow played in ischemic cell death.[5] Results of studies of this type in many laboratories, taken together, established that canine coronary arteries generally were not end arteries and validated the anatomic studies that showed that the various arterial beds of the heart were interconnected in the subepicardial zone by arterioles and often by small arteries[8] but not by capillaries.[9] The arterial connections varied in size from dog to dog, with the result that the volume of collateral flow varied. Thus, dogs with large connections had abundant collateral flow while those with small connections had lesser degrees of flow. In virtually all instances, a subendocardial to subepicardial gradient of flow was present such that the subendocardial layer of the heart received the least and the subepicardial layer the most collateral flow.[5,10] This gradient accompanied the transmural gradient of cell death and is the basis of the general belief that the degree and duration of ischemia are the variables which are most closely associated with the life or death of any given ischemic myocyte. Hemodynamic factors, as well as differ-

(Jennings RB: Treatment of acute myocardial ischemia. West J Med 1987 Jul; 147:62-64)

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Much of the work described in this editorial was supported by National Heart, Lung and Blood Institute grant Nos. HL-23138 and HL-27416.
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ABBREVIATIONS USED IN TEXT

AMPIM = Animal Models for Protecting Ischemic Myocardium
TTC = triphenyltetrazolium chloride

ences in the sensitivity of myocytes in different layers to injury,[11] also contribute to variation in the timing and extent of myocyte death, but the final determinant of survival of individual cells in regional ischemia in vivo appears to be the volume of collateral flow.[4,10]

Failure to recognize the role variations in collateral flow played in infarct size caused much of the variation in results. With small group sizes, it proved to be easy to unintentionally select dogs with low collateral flow and big infarcts in the control group and high collateral flow and small infarcts in the treatment group, especially if the treatment selectively killed off dogs that would have had big infarcts. Much of the remaining variation was due to failure to recognize that the size of the ischemic bed—that is, the amount of myocardium at risk of dying varied from animal to animal. Again, variation was random but was controllable once this variable was recognized. The question of how much necrosis actually had occurred in the ischemic tissue can be answered best by quantitative histologic techniques.[5,10] Although the enzymatic triphenyltetrazolium chloride (TTC) technique underestimates necrosis when the necrosis is focal, it often is used as an unsatisfactory replacement for the slower histologic method. Failure to control for the above variables, together with the use of imprecise, direct or indirect techniques to assess how much cell death actually has occurred, has caused most of the controversy about the effects of therapy in experimental animals.

The National Heart, Lung and Blood Institute supported a study designed to develop appropriate animal models of ischemia in which to test the therapy for acute ischemia—the Animal Models for Protecting Ischemic Myocardium, or AMPIM study. The results of this study established clear guidelines for controlling for variations in collateral flow, infarct size assessment, myocardium at risk and the like.[10] The results of this cooperative study validated methods which finally allowed an investigator to answer the critical question with respect to therapy for acute ischemia: how big would an infarct have been in a heart had no intervention been given?[10] Unless all necrosis is eliminated by the treatment, the variables identified in the AMPIM study should be controlled in any test of the effect of therapy on acute ischemia.

The difficulties I have just described relative to the treatment of acute ischemia in animals in experiments apply to humans as well; however, the human physiology is even more complex. The critical question in humans is the same as it is in experimental animals: how much of the myocardium at risk would have died had an intervention not been given? At present, this question cannot be answered in humans. As in animals, arterial collateral flow is a significant variable; moreover, human hearts exhibit a wide range of collateral development. The hearts of young humans without coronary artery disease have very few collateral connections. They are much like the hearts of pigs[11,12] and probably respond to acute proximal occlusion of a major coronary artery just like the heart of a pig—that is, with transmural severe ischemia and transmural necrosis. Once significant coronary artery disease appears, however, the human heart changes its collateral flow pattern to one much more like that of the dog heart except for the fact that diffuse coronary artery disease often is present and may depress the volume of arterial flow through the collaterals. At any rate, in humans as in dogs, occlusion of a coronary artery usually results in necrosis in the subendocardial region with variable amounts of necrosis in the midepicardial and subepicardial myocardium.[13]

Because of the difficulty of estimating the degree of collateral development in a given patient with ischemia, reperfusion therapy is being tested without an easy or, perhaps, any means of estimating what to expect following occlusion. Is a patient's coronary arterial tree like that of a pig or like that of a guinea pig, in which collaterals are so large that infarcts do not develop after major vessel occlusion?[12] It seems likely to me that reperfusion therapy will not work in patients in whom no collaterals are present unless it is applied very shortly after the onset. On the other hand, more living ischemic myocardium will be available for salvage and for a longer period of time if greater collateral flow is present. This variation in the endogenous condition of the arterial vasculature of the heart makes it difficult to assess the benefit of therapeutic interventions during acute ischemia in dogs and undoubtedly contributes to an even greater variation in the response of patients with coronary artery thrombosis to treatment.

The amount of time during which reversibly injured myocytes are available for salvage by reperfusion is not known in humans and, as indicated, will vary with the volume of collateral flow, hemodynamic and other factors. I have no doubt that moderately ischemic myocytes can be salvaged by successful reperfusion as long as reperfusion has been achieved early enough. If data from reperfusion of animal hearts are transferable to humans, the amount of time during which myocytes can be salvaged is short. Carefully controlled studies in dogs have shown that most myocytes that are going to die in a zone of ischemia are dead after three hours of ischemia have passed and that little or no myocardium is salvageable after six hours of ischemia.[5] Because a dog anesthetized with pentobarbital for an open-chest procedure usually has a high heart rate, elevated blood pressure and so forth, it seems likely that the time available for salvage might be slightly greater in humans than the outer limits given in dogs.

The question of whether reperfusion of myocardium in which no salvageable myocytes are present causes either benefit or additional damage to the heart has not been answered with certainty. The vasculature dies somewhat later than the myocytes, with the result that hemorrhage appears in those parts of the center of the ischemic bed that have been successfully reperfused. Such hemorrhage appears neither to enhance injury nor to depress function in a dog heart. In addition, mildly ischemic myocardium may be present in the heart. Mildly ischemic tissue generally does not die but is nonfunctional and may be electrically unstable as long as the ischemia persists. For example, in dog hearts in which there is significant collateral flow,[5] 20% to 30% of the ischemic myocardium at risk generally survives whether or not the tissue is reperfused. Successful reperfusion of this mildly ischemic tissue will not salvage it in the sense of preventing its death, but will restore aerobic metabolism and contractility and likely remove it as a source of arrhythmias. In the report in this issue, Weiss emphasizes the desirability of restoring ischemic myocardium to an electrically stable state. To the extent that this is achieved in late reperfusion by stabilizing mildly ischemic cells, reperfusion should reduce mortality. Moreover, as noted by Tillisch, results of randomized trials

show less late mortality in the reperfused group of patients. Thus, in addition to salvaging myocytes at risk of death, reperfusion may restore the function of mildly ischemic myocytes that probably would have survived even if no treatment had been given.

The techniques under development by Schelbert and others may yield an objective means of showing that salvage has occurred in successfully reperfused myocardium, especially if the damaged myocytes develop a distinctive metabolic state for which there is an isotopic marker. It is known that reversibly injured myocytes are edematous, have depleted glycogen as well as nucleotide pools[14] and appear to tolerate longer periods of ischemia if the tissue is subjected to repetitive episodes of ischemia separated by periods of reperfusion.[15] Among these various changes might be one which is sufficiently distinctive to allow objective recognition of the fact that living reversibly injured myocytes are present in human myocardium that has been reperfused.

The molecular and physiologic changes developing in ischemia are reviewed briefly by Langer. Although an enormous amount of effort has been directed at identifying the molecular change or changes that cause the cells to die, the precise cause remains unknown. Most of what is known has been developed in studies of totally ischemic myocardium in various in vitro preparations or in severe ischemia in vivo. If the molecular mechanism associated with the transition to lethal injury were known, it might be possible to design a drug specifically to prevent or delay this change and thereby prevent or delay cell death. Even though we lack specific knowledge to design the ideal drug, empiric studies have shown that it is possible to delay the death of severely or totally ischemic myocytes in vivo, such as with cardioplegia, or by pretreatment with agents such as calcium channel blockers.[10] If an agent that would delay cell death could be given prophylactically to the population at risk of infarction, it would allow more time for definitive interventions such as thrombolysis or an emergency bypass procedure.

Knowledge of the biologic changes occurring in zones of moderate-flow ischemia remains scanty. This is the tissue that Buckberg suggests in this report can be salvaged to a greater extent than is possible with restoration of arterial flow alone. In a series of elegant experiments, his group has shown that the degree of functional improvement achieved after episodes of the total ischemia in the K^+-arrested hearts (cardioplegia) can be improved significantly by selective modification of the reperfusate. The modifications have been designed to attack various problems known to be present in ischemia such as cell swelling, excess Ca^{2+} entry, altered capacity to make high-energy phosphate and so forth. He describes treatment of acute regional myocardial ischemia in bypassed hearts using a similarly modified fluid to reperfuse the acutely ischemic myocardial tissue and reports substantial improvements in contractile function of the damaged tissue in hearts subjected to two, four or six hours of regional ischemia. Also, less necrosis was reported to be present when the damaged myocardium was stained with the TTC reaction.

Although the results of these studies appear promising, they do not prove that modification of the circumstances of reperfusion can salvage myocytes that would die if reperfused with unmodified arterial blood. The same problems of collateral flow, myocardium at risk, the use of TTC and the like that have plagued many other workers in this field need to be addressed in these experiments. They should be repeated in a carefully designed protocol that accounts for the previously described chief variables affecting infarct size.

Myocardial ischemia remains an extraordinarily complex phenomenon that is understood only partially. Progress in therapy, however, is encouraging in both humans and animals. The report is very perceptive and summarizes selected aspects of this progress in an authoritative fashion.

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Biochemical and Clinical Aspects of Amyloidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

MARVIN H. SLEISENGER, MD:* *At this conference, we are going to hear about amyloidosis. To set the stage we have asked Dr Diane Havlir to present a patient.*

DIANE HAVLIR, MD:† The patient, a 57-year-old Asian woman, was referred from another hospital because of abdominal pain. She was in her usual state of good health until six weeks before admission when melena, diffuse abdominal pain, anorexia and paresthesias of both hands developed. She was found to be anemic and was transfused with three units of packed red cells. An abdominal computed tomographic scan showed a thickened wall of the ascending colon, and a barium enema revealed narrowing in the ascending colon and cecum, with an ileocecal fistula. Colonoscopy disclosed an indurated and nodular mucosa, and a biopsy specimen showed inflammatory changes and eosinophilic infiltrates. Prednisone and sulfasalazine therapy was initiated, as well as isoniazid, but her symptoms worsened, and a 9-kg (20-lb) weight loss ensued. She was admitted to the University of California, San Francisco, for further evaluation.

Her pertinent medical history included tuberculosis in 1969, for which she received three months of treatment with an unknown regimen. She was born in mainland China, moved to Hong Kong 18 years ago and to the United States 7 years ago. There was no recent exposure to tuberculosis.

On physical examination the patient was thin; her blood pressure was 118/70 mm of mercury, temperature 37°C (98.6°F) and the pulse 80. Her face showed periorbital fullness without purpura. Her lungs and heart were normal. The abdomen was soft with normal bowel sounds, and there was mild right upper quadrant tenderness; there were no masses or hepatosplenomegaly. There was no peripheral edema, but decreased pinprick sensation was noted in a glove distribution in both hands. There were no other neurologic abnormalities.

Her electrolytes were normal. The hematocrit was 29%, leukocyte count 12,000 per μl with a normal differential, platelets 388,000 per μl. A stool specimen was positive for occult blood. Liver function studies were within normal limits; the serum calcium level was 8.9 mg per dl, albumin 2.1 grams per dl, total protein 2.9 grams per dl and erythrocyte sedimentation rate 54 mm per hour; prothrombin time and partial thromboplastin time were both normal. Analysis of urine showed trace protein. Her electrocardiogram showed no abnormalities, and a chest x-ray film showed small biapical fibronodular densities with retraction. After admission the patient's hematocrit fell slowly and she required transfusion of two units of packed red cells. Repeat colonoscopy to within 20 cm of the ileum showed friable and edematous mucosa. Roentgenograms of the upper gastrointestinal tract with small bowel follow-through showed pronounced thickening through the jejunum and ileum, with nodular mucosa. A biopsy specimen of the colon stained positive with Congo red. Stains and cultures of stool specimens for acid-fast bacilli were negative. Serum and urine protein electrophoresis disclosed a γ spike that was further characterized as immunoglobulin G λ in a quantity of 2.6 grams per dl. Sheets of plasma cells, granulocytic hyperplasia and amyloid deposition were observed on a specimen of bone marrow. A series of skeletal x-ray films was normal, as was an echocardiogram.

The creatinine clearance was 61 ml per minute and a quantitative 24-hour urinary protein was 2.8 grams. A 72-hour fecal fat collection was normal. Her private physician instituted melphalan and prednisone treatments after discharge, and she has only required two units of transfusion in the ensuing four months.

DR SLEISENGER: *Thank you, Dr Havlir. It is a pleasure to introduce my colleague, Dr Lawrence M. Tierney, Jr, who will discuss the biochemical and clinical aspects of amyloidosis.*

LAWRENCE M. TIERNEY, JR, MD:* I will start with a definition and classification of amyloidosis, consider its biochemistry and review the clinical aspects of this illness. Reference will be made to the patient presented here so capably by Dr Havlir. Apropos that, had I seen this patient, amyloidosis would not have been high on my differential diagnostic list, and I think it was prudent to treat her initially for tuberculosis and Crohn's disease until further diagnostic studies were done.

We may define amyloidosis as a condition in which one of a number of relatively insoluble proteins is deposited extracellularly in tissues in one or more organs. Dysfunction of these organs may result from pressure necrosis and atrophy of the normal cells. Further, ischemia may occur if amyloid is deposited within blood vessels, even if the tissue itself is free of the substance. There is a diagnostic stain, Congo red, that produces (when viewed with a polarized light source) a green birefringence in affected tissue. Congo red has been available

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(Havlir D, Tierney LM Jr: Biochemical and clinical aspects of amyloidosis [Medical Staff Conference]. West J Med 1987 Jul; 147:65-70)

for about 100 years and is most useful in the cotton industry. It and various derivatives allow cotton to be stained different colors without chemical changes, and so it enjoys significant use in the manufacture of clothing. There is some similarity biochemically between cotton and amyloid that allows these substances to take up the stain. Historically, it appears that amyloidosis was first observed in the 1600s by Bonet, and Rokitansky later observed at postmortem examinations that patients dying of tuberculosis and syphilis occasionally had livers that he felt resembled lard. Virchow, thinking this substance was starch, termed it amyloid, meaning starchlike.[1,2] We now know that this term is a malapropism, but one that will be permanent. The first clinical case was reported 100 years ago; amyloidosis as a primary disorder and its association with multiple myeloma were not appreciated until the early 1900s. Modern investigation into the subject has resulted in a number of elegant biochemical analyses and thorough clinical reviews.[1-9]

Epidemiologically, amyloidosis in any form is rare, and there is no way of knowing its incidence; this is particularly true for "primary" amyloidosis when no other identifiable disease is present. In patients with multiple myeloma, such as the one presented here, perhaps one in ten will show symptoms, signs or laboratory abnormalities ascribable to amyloid deposition and unrelated to those of the myeloma. The third principal form of amyloidosis, that which has been referred to as secondary, may complicate any number of inflammatory illnesses, such as rheumatoid arthritis,[10] leprosy and many similar indolent inflammatory conditions, in between 1 in 20 and 1 in 4 cases.[10] The incidence depends on how it is sought; for instance, the figure in living patients is much lower due to sampling error of biopsies than that found at postmortem examinations, where asymptomatic histologic amyloid may be found and where all organs are studied. In the United States, "secondary" amyloidosis appears to be becoming less common as better therapies for the instigating problems are being developed[10] and represents only a small percentage of the total number of cases of amyloidosis in a recent large series reported from the Mayo Clinic.[1]

As more is becoming known about the diverse pathogenesis and biochemistry of this problem, an alternative clinical classification is to consider amyloidosis as either generalized or localized. Generalized amyloidosis, of which the case presented here is one example, would include "primary" (no other disease present), myeloma-associated and "secondary" (chronic inflammatory disease-related and the amyloidosis of familial Mediterranean fever). Under the category of localized amyloidosis are included instances of discrete deposits of amyloid in single organs of otherwise healthy people, very rare heredofamilial types manifested only by polyneuropathy, senile cardiac amyloidosis and the amyloid that appears in the cerebral vessels of normal older patients but is also an essentail component of the plaques noted in the brains of patients dying with Alzheimer's disease. In generalized amyloidosis, it is now recognized that "primary" amyloidosis represents an expression of plasma cell dyscrasia, and that the pathogenesis, structure of the amyloid and clinical presentation are identical with those of "myeloma-associated" amyloidosis. In contrast, the chemical nature of secondary amyloid is quite different, though there are many clinical similarities to primary and myeloma-associated disease. The composition of amyloid in each of the localized forms of the disease noted also differs.

With these observations, we may proceed to a more detailed assessment of the microstructure of amyloid.

As already stated, amyloid stains eosinophilically with hematoxylin and eosin, appears amorphous and is extracellular when viewed by light microscopy (Figure 1). It also shows an affinity for Congo red, with apple-green birefringence if polarizing filters or lenses are used. Amyloid when observed under the electron microscope, however, is made up of fibrils that are about 10 nm in length and that do not branch (Figure 2). The fibrils are associated with a glycoprotein composed of globular subunits and shaped like a doughnut. It is the fibril that is most important, however, and subsequent mention of the associated globular protein will not be made. Biochemical analysis discloses that all amyloid deposits are examples of what are called fibrous proteins, of which many exist in nature, despite not being numerous in mammalian systems. These various proteins are arranged spatially in two ways; one is in the form of an α-helix, and the other a β-pleated sheet. Amyloid fibroprotein is arranged in the latter. To conceptualize this appearance, one can simply think of

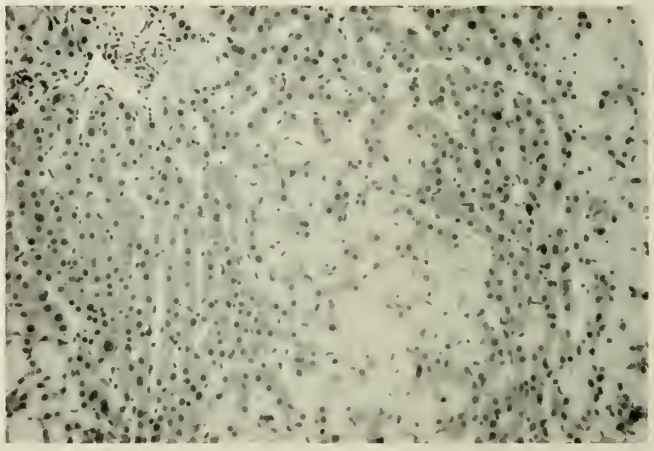

Figure 1.—Photomicrograph of liver showing infiltration of amorphous, extracellular amyloid protein (reduced from magnification ×30).

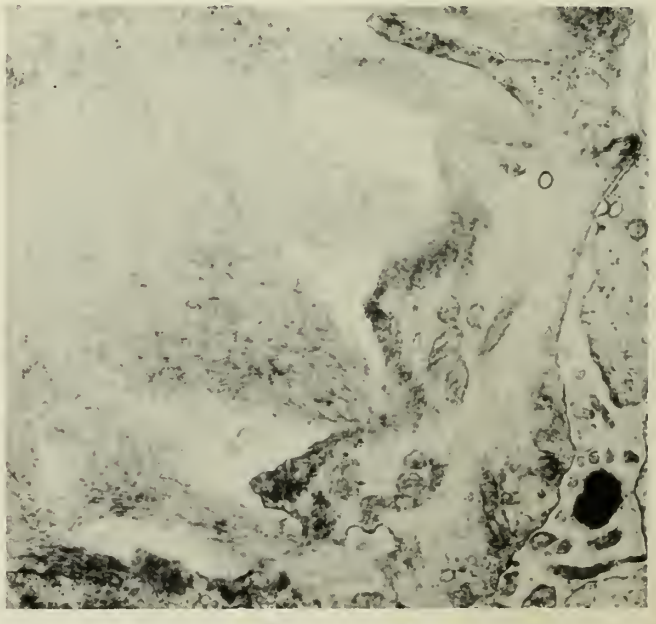

Figure 2.—Electron microscopy of kidney shows amyloid fibrils throughout upper left portion of field (reduced from magnification × 2,000; courtesy of William Isenberg, PhD).

TABLE 1.—*Physicochemical Properties Specific for Amyloid*

Apple-green birefrigence of tissue stained with Congo red when viewed by light microscopy with a polarized lens
Rigid fibrils without branches 10 nm wide by electron microscopy; fibrils are composed of filaments twisted parallel to long axis of the fibril
Fibrils composed of amino acid chains perpendicular to long axis of fibril with a β-pleated conformation when studied by x-ray diffraction
Electron microscopy also shows a second protein, appearing as doughnut-shaped structures consisting of five globular subunits

what an accordion looks like because this is quite similar to β-pleating. At this ultrastructural level the differences in amyloid become apparent, namely, the differences in amino acid sequencing. Amino acids go back and forth across the long axis of the pleats, but despite differing sequence, all amyloid studied to date has been congophilic fibroprotein arranged in this conformation. This description obviously does not identify the amino acids, and indeed the amino acid sequencing is rather different in the various forms of amyloid, as will be discussed. Thus, it is the β-pleating that imports the staining characteristics, and not the amino acid sequence. In a word, because of this biochemistry, different proteins look identical histologically (Table 1).

What is the composition and origin of these differing types of amyloid? Most is known about generalized amyloid, especially primary and myeloma-associated, which may be considered as one for the purposes of this discussion. It has been shown that the fibrillar component of this amyloid consists of a segment of the light chain of the immunoglobulin molecule, specifically its variable portion; it is referred to as AL. The fact that patients in whom monoclonal light chains of immunoglobulin were elaborated would have the development of clinical amyloidosis was proved in a patient when a segment of the same protein identified in serum was later sequenced from amyloid in the patient's tissues.[11] Notably, in patients in whom primary amyloidosis develops without clinical evidence of myeloma, it is the λ chain rather than the $\varkappa$ that is more commonly found; this is the reverse of the light-chain ratio observed in patients with myeloma without amyloidosis. It is unexplained why amyloidosis develops in only 10% of patients with myeloma, perhaps surprising in view of the fact that a much higher percent of myeloma patients have very high serum and urine concentrations of monoclonal light chains.

The amyloid precursor in generalized amyloidosis associated with chronic disease (secondary amyloidosis) is completely different and is not an immunoglobulin. Indeed, this precursor is likely a protein called serum amyloid protein (SAA).[1,2,5] It is a typical acute-phase reactant, meaning it is synthesized by the liver in a variety of clinical states characterized by inflammation, either local or systemic. It consists of 104 amino acid residues having a molecular weight of about 11,500 and associated with a larger high-density lipoprotein. Interleukin 1 appears responsible for initiating the hepatic synthesis of SAA.[12] This is the same protein precursor found in animal models of experimentally provoked amyloidosis and the progenitor of the amyloid of familial Mediterranean fever. Because of its properties as an acute-phase reactant, SAA is found in elevated serum concentrations in numerous patients during many types of clinical illness. Indeed, these concentrations may increase by a factor of 100 in acutely ill patients. If one then examines those very few patients with chronic inflammatory illnesses in whom amyloidosis develops, their tissue deposits show homology of amino acid sequence to SAA; 28 amino acids split off the circulating protein, however, leaving a 76-amino acid fragment as the fibroprotein in most human secondary amyloid deposits. This is referred to as amyloid protein AA. Finally, in even more uncommon types of amyloidosis (see below), prealbumin and other proteins may act as the precursor.

If the forerunner proteins are so ubiquitously elevated, why is clinical generalized amyloidosis due to chronic inflammation so uncommon, as is also the case for generalized amyloidosis associated with myeloma? There must be an abnormality in the processing and catabolism of these proteins. Perhaps tissue macrophages partially responsible for such proteolysis are impaired for this function. It is possible that partial proteolysis removes hydrophilic segments of the light chain (primary), the serum amyloid protein (secondary) or other precursor, leaving hydrophobic and thus highly insoluble remnants behind. When the latter proteins assume the β-pleated conformity described above, they stain positively for Congo red, despite chemical dissimilarities (D. Colby, PhD, oral communication, November 1986). In any event, deposition and clinical illness results from abnormal processing of proteins themselves not structurally abnormal or pathogenic.

Clinically, when does one suspect amyloidosis, and how is it assessed? These comments relate principally to generalized amyloidosis, though the manifestations of a few types of localized amyloidosis will be briefly considered where relevant. It has been taught traditionally that the distribution of amyloid deposition throughout the body allowed one to determine if a patient had "primary" or "secondary" amyloidosis. As more has been learned about the biochemical characteristics of amyloid and as the plasma cell dyscrasia origin of "primary" disease has been secured, it has indeed been found that the patterns of distribution, and thus clinical symptoms and signs, vary somewhat with the origin of the amyloid. In individual cases, however, any pattern may be encountered, and with any case of generalized amyloidosis, the features of the associated processes alluded to may deflect a clinician from its consideration. What follows is an overview of the most-often-encountered manifestations of primary/myeloma-associated and secondary amyloidosis, and a subsequent consideration of amyloidosis in a "review of systems" fashion, without respect to origin (Table 2).

Looking first at what is primary or myeloma associated, epidemiologic data add to the biochemical data suggesting plasma cell dyscrasias. Both occur in older patients, with greater than 95% of patients older than 40 years, and both are more common in men. Virtually all patients without multiple myeloma nonetheless have a monoclonal immunoglobulin in their serum or their urine (albeit in smaller concentrations than seen in myeloma) and increased plasma cells in the marrow. If myeloma is present, it is clinically similar to that disease when it is not associated with amyloidosis. Macroglossia because of infiltration of amyloid is typical. Peripheral neuropathy, symptomatic chiefly as distal extremity pain, is caused by soft tissue deposits, but similar symptoms in the median nerve distribution may be due to its entrapment by infiltrated carpal ligaments. Purpura is a manifestation of primary/myeloma-associated amyloidosis as well because the skin is often infiltrated. Light stroking with a pencil or even a fingertip is enough often to produce it, as is dependency—such as periorbital postproctoscopic purpura. The heart is

TABLE 2.—*Clinical Features of Generalized Amyloidosis**

Primary/Myeloma-Associated	*Secondary*
Affects mainly older men	Epidemiology depends on inciting disease
Purpura common	Skin may be spared
Joint infiltration, carpal tunnel syndrome and peripheral neuropathy prominent	Arthralgias may be present, but objective findings uncommon
Albuminuria common; associated monoclonal light chain often found in urine	Albuminuria may be striking; no urinary monoclonal proteins
Hepatosplenomegaly found often; other GI tract involvement may be equally important clinically	Hepatosplenomegaly ubiquitous and impressive; rest of GI tract commonly involved also
Macroglossia	Tongue usually normal
Adrenals most often spared	Adrenal glands typically infiltrated histologically
Factor X deficiency	Clotting studies normal
Restrictive cardiomyopathy	Heart may be involved, but less commonly

GI = gastrointestinal

*Note that in individual cases, distribution alone seldom allows this separation.

involved by a cardiomyopathy characterized physiologically by diastolic dysfunction; it accepts poorly any increased flow of blood and mimics other forms of restrictive cardiomyopathy and constrictive pericarditis. Also encountered is a joint infiltration similar in appearance to rheumatoid arthritis but without true synovitis. Acquired factor X deficiency is another cause of a bleeding diathesis in many of these patients; it is speculated that there is an affinity of some types of amyloid precursors for factor X, and the complex is removed from the circulation entering the tissue deposits.[13] Hepatosplenomegaly, though encountered, is less prominent in primary/myeloma-associated amyloidosis, and the same is true for glomerular infiltration and consequent albuminuria with nephrotic syndrome.

We turn next to secondary amyloidosis, the epidemiology of which in turn reflects that of the diseases responsible for producing it. In this country, rheumatoid arthritis, seronegative spondyloarthropathy, bronchiectasis, osteomyelitis and infected decubitus ulcers are possible causes. Certain tumors, especially those associated with fever, interleukin 1 production and consequent elevation of SAA (hypernephroma, lymphoma), can also be associated with secondary amyloidosis. Intravenous drug abuse may also lead to this problem. The typical clinical picture in secondary generalized amyloid is dominated by the renal abnormalities, with the development of proteinuria and the nephrotic syndrome in a patient with chronic inflammatory illness. Hepatosplenomegaly is ubiquitous and more impressive than it is in primary/myeloma-associated amyloidosis, though overlap occurs. Features usually absent in secondary amyloidosis include macroglossia, dermal infiltration with purpura, peripheral neuropathy, carpal tunnel syndrome and synovial infiltration. Of note, the adrenal glands are nearly always histologically involved, although clinical adrenal insufficiency does not occur.

Localized amyloidosis may take many forms. Isolated cardiomyopathy in the elderly is a common example. Though less well studied chemically, it appears that the precursor protein may be prealbumin, in distinction to primary or secondary amyloidosis. Amyloid deposits are often noted in a thyroid gland affected by medullary carcinoma; these deposits are likely derived from calcitonin. Several familial types of amyloidosis resulting in polyneuropathy have been recognized in various parts of the world. The precursors responsible differ but may include prealbumin, γ-trace protein and possibly others. These familial disorders are vanishingly rare in the United States. Not rare, however, is Alzheimer's disease, and there is much interest in the observation that the senile plaques in this disease have an amyloid core. The origin of this amyloid may be local, representing degenerated neuronal processes, or could reflect trapping by abnormal neurons of circulatory precursors. It has been suggested that this amyloid is a multimer of a 4,000-dalton peptide different from light chains, serum amyloid protein or prealbumin.[14-16] It is similar if not identical to the amyloid found in cerebral blood vessels in many patients with Alzheimer's and also in elderly patients with a normal mental state. This amyloid angiopathy is in turn associated with cerebral hemorrhage in older patients who otherwise have no risk factors for this problem. This hemorrhage differs from others in having lobar rather than specific large vessel distribution, and may recur in other locations in the brain.[17]

A recently recognized type of localized amyloidosis is the carpal tunnel syndrome observed in patients on long-term hemodialysis. This may occur in as many as 5% of patients on long-term dialysis, irrespective of the cause of the underlying renal disease. Here the amyloidogenic protein shows amino acid sequence homology to β_2-microglobulin. It has been speculated that inefficient dialytic removal of this protein results in its accumulation, but as in other types of localized amyloidosis, its tropism for this anatomic site is unexplained.[18]

A final example of localized amyloidosis might be termed the "amyloidoma." Here amyloid, usually of light-chain derivation, occurs locally in the form of a mass, for instance in the breast or lung, without any evidence of current or subsequent systemic plasma cell disease. It has been speculated that there is local production of light-chain-type amyloid in affected areas. Macrophages may synthesize it, or, alternatively, local catabolism by these cells is impaired. The importance of "amyloidoma" relates to its mimicry of primary or metastatic malignancy.[19,20]

It might be appropriate now to summarize the clinical effects of amyloid by system, remembering that the physical presence of the substance and not its chemistry determines symptoms.

In the skin, amyloid has an unexplained predilection for the face and trunk; alopecia, in addition to purpura, may occur. The dermis may resemble that seen in progressive systemic sclerosis; 40% of patients with primary amyloidosis are affected. There is also an unrelated rare localized form, lichen amyloidosis, manifested as coalescent papules on the extensor surfaces of the lower extremities.

In the heart, amyloidosis, whether isolated there or part of a generalized syndrome, causes the restrictive cardiomyop-

athy described above. Other features include low voltage on electrocardiography and a granular sparkling appearance on two-dimensional echocardiography. The myocardium is more affected than the conduction system, so that pump dysfunction is more prominent than rhythm disturbance. Of interest, when the coronary arteries are involved in addition to the myocardium, clinical symptoms are more likely to occur. Cardiac symptoms may be aggravated by preexistent coronary atherosclerosis or hypertension, which are common in this age group. Many elderly patients with cardiac amyloid at autopsy, however, are free of complaints during life. Digitalis intoxication is said to be more common in patients with this disorder, but this may be a reflection of more aggressive use of the drug as a consequence of poor therapeutic response, which might be expected in light of the pathologic features.

Amyloidosis as a solitary lesion (amyloidoma) may present as a pulmonary coin lesion. Isolated deposits at various other locations in the respiratory tree may result in epistaxis, hoarseness and localized wheezing. Likewise, in rare cases of primary/myeloma-associated amyloidosis there may be diffuse infiltration throughout the lungs, producing a severe interstitial pneumonitis. Lung parenchyma, airways and vessels all may be involved. Pulmonary amyloidosis may also be noted histologically in patients with otherwise isolated cardiac amyloidosis.[21]

The gastrointestinal tract also may be involved in numerous ways.[22-24] Macroglossia has already been alluded to; it can be difficult to diagnose, although patients often are aware of an increase in size. Dysfunction of many types in any part of the gut is possible. Motility may be impaired, as both the submucosa and muscularis are infiltrated; autonomic neuropathy contributes. Malabsorption when present is due to bacterial overgrowth analogous to that seen in scleroderma. The mucosa itself is usually spared. There may be achlorhydria and in fact vitamin B_{12} deficiency. Most relevant to the patient described earlier is the mimicry of inflammatory bowel disease; fissuring of the type seen here is reminiscent of Crohn's disease. Ulceration at any site may cause gastrointestinal hemorrhage. Symptoms of abdominal angina occur if mesenteric vessels are infiltrated, and protein-losing enteropathy is possible. Intestinal obstruction may result from an amyloidoma. Pseudo-obstruction also occurs given the motility problems. The liver (and spleen) may be enlarged, sometimes enormously, and the alkaline phosphatase level is elevated disproportionately to the bilirubin level. A characteristic appearance on liver scan may be seen in these patients in which there is much uptake in the liver and marrow, not unlike that seen with cirrhosis, but the spleen is normal. Finally, the rectum often contains amyloid histologically, an observation used in establishing the diagnosis. Though the incidence of gastrointestinal involvement is uncertain, it occurs with similar frequency in primary/myeloma-associated and secondary amyloidosis. As noted, hepatosplenomegaly is more prominent in the latter. It is noteworthy that the patient under consideration presented with gastrointestinal complaints. This shows the relative lack of usefulness of the first symptom in such a pleomorphic disease process. Given such wide clinical variation, few patients with amyloidosis are "classic."

In the kidney, albuminuria is the major manifestation, but not light-chain proteinuria unless there is associated myeloma. This is due to the predilection of amyloid for the glomerulus, although basement membrane infiltration can produce nephrogenic diabetes insipidus, and lower tract infiltration may lead to hematuria. The urinary sediment is otherwise nonspecific. Sterile pyuria and microhematuria may be present, but are minimal; occasionally granular casts are observed. Renal failure occurring over one to two years is the commonest cause of death from amyloidosis. It occurs in primary and secondary types and, in the former, may complicate renal injury induced by other mechanisms when myeloma is present. Though it is taught classically that large kidneys are typical of this problem, this is by no means universal, and they may regress in size as renal failure advances.[2]

Amyloid infiltration of the joints occurring in patients with primary/myeloma-associated disease is unusual but impressive. A patient may appear to have "shoulder pads," and hands and knees may also be involved. Though true synovitis is absent, morning stiffness and subcutaneous nodules may suggest rheumatoid arthritis, as may the constitutional symptoms shared by patients with both illnesses. When joint effusions are present, they have been noted to be xanthochromic.[2]

Finally, mention has been made of polyneuropathy as a feature of primary/myeloma-associated amyloidosis; familial isolated polyneuropathies may differ clinically, but will not be further considered here. The acquired neuropathy is both sensorimotor and autonomic; sensory symptoms and signs are more prominent than motor. Histologically, deposits are found in ganglia, rootlets, nerves and in dural blood vessels. A recent study of sporadic, idiopathic amyloid polyneuropathy in several patients without evidence of myeloma or systemic amyloidosis indicated that the deposits were of light-chain origin.[25] Most cases of amyloidosis with neuropathy, however, occur with generalized disease, either primary or myeloma-associated. Median nerve entrapment from carpal tunnel syndrome may also be associated and is also observed without systemic amyloidosis in patients on long-term hemodialysis.

The diagnosis once amyloidosis is considered is not difficult. In generalized disease (primary/myeloma-associated or secondary), rectal biopsy will have the highest yield, nearing 80% to 85%. Gingival biopsy is also sensitive. Otherwise, biopsy of clinically affected and accessible tissue is prudent. Fears about fracturing the kidney and liver are largely unfounded and relate to the earlier use of much larger needles for organ biopsy. Appropriate assessment of clotting is necessary, however, because of the bleeding tendency if factor X deficiency is present. Electron-microscopic identification of amyloid fibrils in the urinary sediment is not specific; subcutaneous fat aspirates showing them are.

Congo red staining of any tissue is necessary to establish the diagnosis of amyloidosis, but this may not be routinely done. Thus, clinicians must maintain a high level of awareness of amyloidosis in patients with obscure polysystemic illness, and must not forget it even when other diseases seem more likely. Again, the case presented here provides an excellent example of this dictum. Once amyloidosis has been histologically established, electrophoresis and quantitation of serum and urinary immunoglobulins, as well as bone marrow aspiration, are indicated, particularly in the absence of a chronic inflammatory condition. The parallel diagnosis of multiple myeloma has implications for treatment, as also is shown by this patient.

The results of therapy are disappointing in amyloidosis of any origin. Obviously patients who have myeloma-associated amyloidosis should receive the same chemotherapy given for

myeloma, as was done for our patient. That being said, the presence of amyloidosis in patients who have multiple myeloma worsens an already poor prognosis, despite therapy, and it was encouraging to hear that this woman has done well for several months. In primary amyloidosis without multiple myeloma, cytotoxic therapy makes at least intuitive sense given the origin of the amyloid. There is some interest in the use of colchicine in secondary amyloidosis, especially when associated with familial Mediterranean fever; this may be of most value when it is given prophylactically (1 to 1.5 mg a day). It appears to reduce attacks and their severity. Colchicine has minimal or no effect in other forms of secondary amyloidosis, but retards its development in some experimental forms. Even treatment of the underlying disease seldom leads to diminution of deposits, though there are sporadic examples of this occurring. Finally, renal transplant is effective in selected patients with predominant renal involvement, with only slow reaccumulation of amyloid deposition.

In sum, then, amyloidosis is an illness with protean clinical manifestations in which no organ in the body is spared. It serves as an excellent example of a previously idiopathic process whose varied pathogenesis has become less obscure because of the application of modern biochemistry to its mysteries. As a mimic of many other diseases, it should remain in the differential diagnosis of any unexplained local or polysystemic process. Finally, despite the advances in understanding it, treatment remains in large part unsatisfactory.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *How strongly do you feel about cytotoxic therapy for primary amyloidosis without myeloma? It is my understanding through conversations with other centers that there has been little evidence for its efficacy to date.*

DR TIERNEY: I agree that such therapy is purely empiric and arises from the knowledge that this type of amyloidosis is so similar in origin to multiple myeloma. It may be that the more aggressive therapies being applied to myeloma will have some future role in primary amyloidosis without myeloma, but additive toxicities will also have to be reckoned with.

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Epitomes
Important Advances in Clinical Medicine

Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Current Perspectives in Posttraumatic Stress Disorders

THE TERM POSTTRAUMATIC STRESS DISORDER was first officially used in 1982 and was associated with the problems of Vietnam veterans. The disorder appears in those who have suffered a significant traumatic event that is outside the usual human experience. These include serious threats to one's life or one's family or relatives or witnessing violence or death. The primary symptoms include nightmares or intrusive thoughts, numbing of responsiveness to the external world and a series of other symptoms that may involve avoidance behavior of the traumatic event, startle reaction, sleep disturbance, memory impairment and guilt about surviving. This disorder has now been studied in a number of survivors.

Following the May 1980 eruption of Mount St Helens in southwestern Washington, a team of researchers studied the effects on persons involved. Of 548 who experienced the volcanic eruption, 99 had a psychiatric disorder related to the eruption. Most had a generalized anxiety disorder, but 11 people had a posttraumatic stress disorder. In contrast to this natural disaster, disasters caused by humans often result in a higher incidence of this latter disorder.

During the Pol Pot atrocities in Cambodia between 1975 and 1979, conditions like the holocaust in Nazi Germany occurred. Researchers found in Cambodians symptoms of the posttraumatic stress disorder similar to those suffered by Nazi victims. In some Cambodians the symptoms have lasted for more than ten years. In studying a community sample of Cambodian adolescents who had endured these atrocities, 20 of 40 students had the disorder. A majority also had persistent depressive symptoms. Recent work with children who have witnessed violence or have been victims of physical abuse or incest show a very high incidence of the disorder. In one study, 80 of 100 uninjured witnesses of violence to parents had posttraumatic stress disorder. Much of the reexperiencing takes the form of traumatic play and dreams. These children often appear numb, constricted and show subdued behavior.

There is increasing evidence that this disorder can be very persistent. In a 40-year follow-up of World War II American prisoners of war, of those who had the stress disorder immediately following the incarceration, 39% still reported mild symptoms, 24% had improved but with moderate residual symptoms and 8% had no recovery or had deteriorated. There are reports of the reactivation of the syndrome with a 30-year delay in veterans of World War II. It can have a prolonged recurrent course, and current stresses such as occur in aging can reactivate it.

People who have histories of being exposed to severe traumas, either as children or adults, should be considered at a high risk for suffering from a posttraumatic stress disorder that may have been asymptomatic for long periods of time.

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Group Therapy and Schizophrenia

GROUP THERAPY is a useful modality for treating patients with schizophrenia. In a recent review of 43 controlled-outcome studies, it was judged to be effective in 80% of the outpatient studies and 67% of the inpatient studies. In the inpatient setting, there was a tendency for long-term groups to be more beneficial than short-term groups, and significantly more interaction-oriented groups were judged effective than insight-oriented groups.

Homogeneous groups composed entirely of schizophrenic patients are more successful clinically than heterogeneous groups because the patients have common treatment goals, and specific techniques can be used that address mutual needs. Inpatient groups usually meet three to five times per week in sessions lasting 45 to 60 minutes. In the outpatient setting, weekly groups lasting 60 to 90 minutes are typical. In both settings, five to eight patients is the optimal number. Cotherapy teams are useful because it sometimes takes two therapists to cope with a group of disturbed patients. Therapists should be active, open, supportive and consistent, and they should strive to create a safe environment free of excessive anxiety and confrontation.

Several clinical studies have found that patients in these groups value discussion topics aimed at improving relationships with others and learning to cope with psychotic exper-

iences. Less valuable have been topics centering on advice-giving and the expression of social amenities. Although personal problems may be discussed, topics dealing with sexual issues and anger between the members may increase anxiety and lead to regressive behaviors.

Schizophrenic therapy groups are cost-effective, they have been found to lower the rates of readmission to hospital and they are valued by patients, with attendance rates of more than 95% being reported. They are an important treatment modality when used in conjunction with antipsychotic medication and long-term follow-up.

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Update on Psychoneuroimmunology

THE RAPIDLY EMERGING interdisciplinary field of psychoneuroimmunology—also called neuroimmunomodulation, behavioral immunology or psychosocial neuroimmunology—is concerned with the complex bidirectional interactions between the central nervous system and the immune system and their clinical implications. Several acute and chronic naturally occurring stresses and depression have recently been shown to be immunosuppressive. The stress of medical school "examination week" activates latent herpes simplex virus infection to a greater degree in lonely students. Activation of the Epstein-Barr virus and lowered helper-suppressor T-cell ratios result from the chronic stress of providing family care to victims of Alzheimer's disease. Poor marital quality, a recent separation and divorce and consequent depression are associated with a reduction of several measures of immune function. Depressive illness requiring hospital admission (but not dysthymic disorders) is accompanied by immunosuppression as shown by reduced lymphocyte mitogenic responsiveness in vitro. Patients with endogenous depression associated with psychomotor agitation show a reduced sensitivity of lymphocyte β-adrenergic receptors. Depressed patients have a lower basal lymphocyte content of cytoplasmic glucocorticoid receptors than controls.

The close relationship between the central nervous system (CNS) and the immune system is emphasized by the findings of receptor sites for some psychotropic drugs on immunologically competent cells and by cell-surface similarities between neurons and lymphocytes. To illustrate, benzodiazepines stimulate monocyte chemotaxis, an effect likely mediated by the peripheral-type receptor. Thy-1 glycoproteins are major cell-surface constituents of thymocytes and neurons. French investigators have implicated lateral specificity in the cerebral cortex in neuroimmunoregulation, with possible cognitive versus affective influences on immunity. Left cortical lesions decrease T-cell numbers, responsiveness to mitogen and "natural killer" cell cytotoxicity. (Autoimmune and atopic diseases are more common in left-handed persons.)

Interest in the role of enkephalins and endorphins in mediating stress effects on immunity has increased considerably. Rats that receive intermittent foot shock stress, which produces opioid-dependent analgesia, show naloxone-reversible immunosuppression. Secretion of both adrenocorticotropic hormone (ACTH) and β-endorphin is controlled by corticotropin-releasing factor (CRF). In turn, the immune system secretes factors that influence CRF and opiocortin neurons. An anatomic substrate in the CNS exists for participation of the peptide systems in autonomic, immune and other physiologic homeostatic mechanisms, which tend to be disordered under conditions of stress, in disease and in aging. Met-enkephalin-like, morphinelike and β- and γ-endorphin receptors have been identified on lymphocytes. ACTH and β-endorphin can both behave like lymphokines. Both γ-interferon and the immunosuppressant drug cyclosporine modify symptoms of naloxone-induced abstinence syndrome in morphine-addicted rats. Edwin Blalock, PhD, at the University of Alabama at Birmingham says "It appears that the immune and neuroendocrine systems have the ability to signal each other through common or related peptide hormones and receptors."

New links are being forged between sleep research and psychoneuroimmunology. Interferon and other lymphokines can enhance slow-wave sleep, and interferon decreases rapid-eye-movement latency, suggesting that sleep may play an important role in recuperative processes. Interleukin 1 levels increase in conjunction with the onset of slow-wave sleep. Such findings suggest that disturbance of sleep, as occurs in conjunction with depression and with stress, might contribute to the associated impairment of immunity.

The organic brain syndrome found in about 40% of patients with the acquired immunodeficiency syndrome (AIDS), a presenting symptom in as many as 10%, is based on the neurotropic and the lymphotropic natures of the human immunodeficiency virus, which infects monocytes and microglia of the CNS as well as other glial cells and neurons. Psychosocial research in AIDS suggests that attitudes, affects, social support and coping may affect the duration of survival. Current psychoneuroimmunologic research in AIDS and the AIDS-related complex should provide more specific clinical and immunologic correlates of psychosocial variables.

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Methods to Aid Memory in the Aged

THERE ARE GOOD NEWS and bad news about improving memory with aging. The good news is that 90% of us will never become demented. The bad news is that the normal memory loss experienced by a typical 75-year-old person is a loss of 30% when compared with their performance during youth. Because there is little to be done about dementia itself, I will discuss improving normal memory losses with aging.

First of all, the terms have been changed. This normal loss used to be called "benign senescent forgetfulness." It was

called benign because no one ever died of it. But this term often led physicians to minimize elders' complaints. Yet a loss of 30% would make most people worry: what was benign for physicians appeared malignant to patients. To underline the seriousness of the problem, the National Institute of Mental Health has given such losses the name "age-associated memory impairment."

What can be done about this memory impairment? First of all, it is important to realize that its psychological causes are at least as important as the biologic ones. The psychological causes include a reduced ability to concentrate, less use of organizational schemes and less use of visual image-based associations. These factors can be remedied.

In a recent review I documented that a series of different types of interventions from a number of independent laboratories has shown statistically significant and long-lasting improvement of function by psychological interventions. These interventions include the use of image associations and organizational schemes (mnemonics), relaxation therapies to reduce anxiety that robs elders of their ability to concentrate and a host of techniques for specific situations, such as reading retention, numbers or absentmindedness. These techniques have been compiled into a workbook that can be used by therapist or patient alike. Using such techniques in the office setting should lead to documentable improvement in function of most elders with age-associated memory inpairment.

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Environmental Sensitivity—Allergic to Everything?

A MEDICAL SUBCULTURE has evolved comprising patients claiming polysymptomatic, multisystem, chronic "allergic" reactions to numerous environmental "excitants" present in food, air, water, drugs, fabrics and many other sources and a group of physicians calling themselves clinical ecologists, who believe their treatments can benefit these patients. Before connecting with clinical ecologists, these patients were frustrated in their often-extensive efforts to find physicians who could say, "I know what's wrong with you and I can help you." The patients are diverse, although several characteristics predominate: most are women in their 30s and 40s, stable employees in service or technical-professional occupations (often medical or high-tech settings) who have education beyond high school. They had been treated for several illnesses, frequently had respiratory allergies, had had viral infections and may have been treated for hormonal irregularities.

The severity of the restrictions imposed on these patients' lives before and after their "diagnosis," both by themselves and by the clinical ecology treatment regimen, is impressive. They very often do not return to work and withdraw from social contacts. They monitor their diet closely and avoid tobacco smoke and perfumed products such as soap, toothpaste and deodorant and extend their restrictions to everyone in proximity. Their almost phobic reactions are triggered by solvents, gas heat and vehicle exhausts. They may wear only "natural fiber" clothing, modify their residences by installing electric heat and removing rugs and drapes or moving to "purer" mountain, coastal or desert locales. Some even carry oxygen tanks and masks when away from their "safe" environments. While they may be labeled, according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, as having "somatization disorder" or "atypical somatoform disorder," all seem to share a sense of "vulnerability" to illness and environmental hazards and the need to simplify and control their lives. Their efforts to avoid the substances they and their physicians deem harmful preclude participating in most work environments and result in declarations of disability.

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Long-term Effects of Terrorism on Children

ALTHOUGH AMERICAN CHILDREN are the frequent targets of violence in the form of abusive injury, they are rarely victims of terrorist attack. Youngsters elsewhere in the world, however, are not so fortunate, and studies of the psychiatric sequelae of terrorism have begun to appear in the literature. Terrorism is the exertion of force threatening annihilation to project a sense of powerlessness on the target population. Its use seems to be increasing, and it is defended as a legitimate means to achieve a desired political objective. In many instances adolescents have assumed the role of combatant and have thereby become the agents of intimidation and destruction.

The pathogenic element of terrorism, apart from any physical injury, is the experience of psychic trauma that results in helplessness in the face of intolerable danger, anxiety and arousal. The susceptibility of any child to psychic trauma is a function of several factors, including genetic, constitutional and personality makeup; past life experiences; age and state of mind, and the content and intensity of the event. In those situations in which children have been held hostage or exposed to a murderous assault, most will suffer the posttraumatic stress disorder. The symptoms of this syndrome for children involve deleterious effects on cognition, emotions, interpersonal relations, behavior and vegetative function. In addition, the developmental phase of the child contributes to the specific constellation of findings. A preschool child is likely to show regression, school-age children often present with somatic complaints and traumatized adolescents commonly display acting-out behavior.

The natural history of the posttraumatic stress disorder in children has not been fully elucidated, but evidence is accumulating that the long-term effects of terrorism can be substantial. Children continue to show posttraumatic play and reenactments, seen as repetitive, unsatisfying activities organized around traumatic themes. Other persistent symptoms include nightmares and night terrors, residual traumatic anx-

iety and memory disturbances such as retained misperceptions of the event and omen formation. In contrast to adults, children are apparently not subject to amnesia or significant denial of the external reality of a violent event. Adolescents, in particular, remain distressed over their vulnerability during an incident. Youngsters may engage in suppressing conscious thoughts about the event as a device to avoid feelings of embarrassment and anxiety. Prominent personality alterations have been reported, including the emergence of "survivor identity" and delinquency. A common finding is an enduring sense of pessimism with a belief in a shortened life expectancy and recurrent dreams of personal death. Some traumatized children have become suicidal or have manifested full depressive episodes. The prognosis for child victims of terrorism will, in a large measure, depend on the family's and community's coping resources and the availability of psychiatric treatment.

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Children at Risk—New Aspects

PREVENTING MENTAL ILLNESS has been at the roots of child and adolescent psychiatry. Its time has come. There will never be enough psychiatrists to care for the mental health needs of the nation. There has been increasing research in the field of risk that has promise for implementing a prevention program. Although correlation is not causation, there is a relationship between risk and a series of spectral outcomes that occur in adolescence and early adulthood. For instance, it has been shown that continued aggressive and asocial behavior in preschool children is a risk factor for later delinquency and that the fetal alcohol syndrome is a predictor of poor school performance and mild mental retardation. Risk factors in children are predictors of a wide variety of later disorders. Common risk factors in families and children are psychotic parents, depressed parents, divorce and parental disharmony, alcoholism or substance abuse in family, conduct disorders, sexual and physical abuse, loss and separation, mental retardation, chronic illness and poverty.

Risk factors that develop in adolescence, such as teenaged pregnancy and substance abuse, may be risk factors for the next generation of children. Significant outcomes for risk factors are substance abuse, delinquency, suicide and homicide, school dropout, teenaged pregnancy, psychoses and depression and learning disabilities.

Children who are victims of natural disasters, such as "acts of God," or those who witness murder, rape or beatings of a parent or sibling are at risk for the posttraumatic stress disorder. Early intervention is essential for prevention. Physicians often see divorced parents or parents who need to be admitted to hospital for mental or physical illness but do not pay sufficient attention to the plight of the children in these situations. Often these children will benefit from counseling or therapy. Research will continue to define risk factors and proper interventions. Preschool day care, early periodic screening and developmental testing are preventive programs that need to be developed. Research and interventive programs will have an impact on the prevalence and incidence of mental illness in our society. Physicians need to be aware of opportunities for prevention.

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Family Involvement in Managing Schizophrenia

SCHIZOPHRENIA is a severe and disabling illness with a prevalence of about 1% around the world. Symptoms include looseness of associations, delusions and auditory hallucinations, which usually begin in the second or third decade of life and in about two out of three patients persist or become more severe throughout life. Antipsychotic medications are effective at controlling some of these symptoms, but their use involves a one in five risk of tardive dyskinesia, and patients often remain less symptomatic but severely impaired in their ability to carry on the activities of a normal life.

Some decades ago, families were thought to be implicated as a causal agent in schizophrenia. It was believed that double-binding communication patterns created the disease in children. Recent research, however, on the genetics of schizophrenia among twins and adoptive offspring indicates a strong but non-Mendelian genetic factor in schizophrenia. Having a biologic parent with schizophrenia raises the risk of getting the disease from about 1% to 7%.

Attention in family research shifted from causation to patient adjustment. A factor identified as "expressed emotion" was found to be predictive of decompensation among schizophrenic patients. This concept had two components: criticism and overinvolvement. More recently, an aspect of family environment that prevents rather than promotes relapse was identified. This variable, with the similar name "expressiveness," consists of a family's tendency to solve problems together rather than separately, to share information. Schizophrenic persons from families with high scores on the expressiveness subscale of the Family Environment Scale are less likely to be readmitted to hospital.

These observations have led to various new interventions with families of persons with schizophrenia variously labeled "sociotherapy," "psychoeducation" and "family therapy." These interventions have been designed to teach families about the illness, the importance of a consistent antipsychotic medication regimen, the warning signs of decompensation, ways to provide consistent structure in a patient's daily activities and means of reducing abrasive contact between patient and family, thereby reducing the hostility and overinvolvement that has been found to provoke decompensation. Several of these studies have shown success in changing the family atmosphere and reducing decompensation. Schizophrenic pa-

tients suffer impairment in their abilities to think and to maintain social relationships. Indeed, their social networks are smaller than those of normal people. It therefore makes sense to develop interventions that help these networks better support their patient members.

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Childhood Depression—A Recent Phenomenon?

ADOLESCENT DEPRESSION and some of its manifestations in violence, anger, suicide and substance abuse have been described and a good deal of research conducted into the etiology, diagnosis and treatment. Only within the past five years or so has any attention been paid to depression in children, with the documentation of both severe depression with suicidal ideation and suicide attempts in young children of primary school age.

In several adolescent suicide studies, an effort to retrospectively study the behaviors and school records of actual suicides has revealed some common diagnostic criteria. Review of the cumulative records of ten suicidal adolescents—that is, actual suicides and severe previous attempts—shows that by the third, fourth and fifth grades there were signs of academic failure, the children were described as loners without friends and almost every teacher described them as looking sad. Parent conferences showed chronic alcoholism of one or both parents or divorce (or both). Death of a parent or sibling was also frequently noted. Histories of child physical and sexual abuse were found in four of the ten cumulative records.

A current review of the indicators of childhood abuse has been important in helping educators to identify children at risk for abuse and subsequent depression or antisocial, angry behavior toward children and adults.

Recently depression has been documented in preschool children in the general population. The Children's Affective Disorder Scale was administered and a parent rating scale given; teachers' observations of sad, isolated or overly hostile children were closely correlated with the results of the tests.

Treatment of children who are depressed has reportedly been successful. Similarly aged children with similar problems have benefited from group therapy with a trained group leader. For very young children, activity or play groups provide peer interaction and tangible signs of adult concern and caring. Family therapy or, at least, work with a parent or parents to demonstrate how caring can be shown by attention to a child's productions of drawings or play is effective in reducing depression. Playing games is often mutually enjoyable to parents and children after the parents have been helped to be playful. Dealing with abusive parents by reporting them to child protective services may or may not remove the abusive parent but should halt the abuse once a child and family are being monitored.

The use of antidepressive medications, especially the tricyclic antidepressants, has proved effective in doses of 25 to 50 mg per day, depending on the size of a child.

We are obviously not talking about childhood depression due to hospital admission for acute physical disease or depression due to dealing with chronic illness like diabetes or life-threatening diseases. Physicians who see children and families can often identify the child who looks sad or despondent or who is nonresponsive to anyone's efforts to engage the child in conversation. At our Children's Psychiatric Hospital where children from age 3 years to 15-year-old adolescents are treated as inpatients, many young depressed patients have been referred by physicians. These are children who have experienced multiple stresses. Some have been abused and have also lost a parent through divorce or death. Many of these children not only appear sad but have great difficulty in trusting adults and have sleeping problems, generally nightmares. Some of these children have retreated into psychotic behavior, hearing threatening voices and staring off into space as if they have visual hallucinations. These children have done well with a combination of antidepressant medications and a caring staff, effective group and individual therapy and an effective special education program that promotes a better self-image through increased competence.

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Antidepressant Treatment for Bulimia

CERTAIN ANTIDEPRESSANT MEDICATIONS, particularly imipramine hydrochloride, desipramine hydrochloride and the monoamine oxidase inhibitor phenelzine sulfate, are useful in treating bulimia, the binge-purge syndrome. Double-blind studies have shown the superiority of an active medication over placebo, whether or not the bulimic patient is clinically depressed. Although as many as 75% of bulimic patients may be depressed, anxiety and personality disorders often coexist as well. The mechanisms of action of the medications are unclear, but may be through effects on anxiety or depression or more directly.

While medications may be effective, individual and group therapies using cognitive-behavioral methods that attend to eating patterns, nutrition and psychological issues have about the same success rate as does the use of medications alone. Nevertheless, several of the medication studies were conducted primarily with patients for whom previous trials of psychotherapy had failed.

The prudent approach to treating bulimia is to provide both psychological and nutritional counseling with a carefully worked out meal plan. If a patient does not improve within

one to two months, antidepressant therapy should be tried. An antidepressant regimen may be started immediately for patients who present with serious depression or for those whose disorder failed to resolve with competent eating-disorders counseling.

The average medication doses are similar to those prescribed for depression—that is, 200 to 300 mg per day of tricyclic antidepressants or full therapeutic dosages of monoamine oxidase inhibitors, such as 45 to 90 mg per day of phenelzine. A small dose is started at bedtime, after a patient is unlikely to purge. The dosage should be gradually raised over the next few days to a therapeutic range. For any of these medications a minimum of six weeks is necessary for an adequate drug trial. Side effects occur with all of the antidepressant medications and may be particularly common with the monoamine oxidase inhibitors.

Trials with several different medications may be necessary. As many as 50% of patients may become asymptomatic. Not every patient will respond, but most will have at least some symptomatic improvement.

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The Dopamine Hypothesis Revisited

THE DOPAMINE HYPOTHESIS of schizophrenia originally proposed that a functional overactivity of the dopamine neurotransmitter system was responsible for the symptoms of schizophrenia. There has been much evidence to support this theory although most has been inferential and not direct in nature. Early work showed a relationship between neuroleptic drugs and central nervous system (CNS) dopamine systems by observing that neuroleptic administration increased the accumulation of dopamine metabolites in rat brain. With the development of sophisticated receptor-binding techniques, it was found that the affinity of individual antipsychotic drugs for the butyrophenone-labeled, non-adenyl cyclase D2 receptor was closely correlated with their potency as antipsychotics. A major criticism of the relevancy of these findings, however, has been the observation that neuroleptic drugs require weeks to months to be maximally effective.

In recent years, preclinical studies have begun to examine the slow-to-develop effects of neuroleptic drugs on CNS dopamine systems. Evidence from both electrophysiologic and biochemical studies comparing short- and long-term administration schedules suggests that dopamine neurons respond differently with different schedules. Short-term administration of neuroleptics results in increased dopamine neuronal firing, whereas long-term use produces substantially decreased rates. Plasma studies of homovanillic acid (HVA), a major dopamine metabolite in humans, have shown a time-dependent relationship between the levels of plasma HVA and clinical symptoms in schizophrenia. Furthermore, a recent positron emission tomography study found that the quantity of D2 dopamine receptors showed a greater increase in both drug-treated and drug-naive schizophrenic subjects than in controls.

This recent evidence supports the dysfunctional nature of the CNS dopamine system in schizophrenia. Current research will provide more answers and expand our knowledge to include systems that interact with dopamine in patients with schizophrenia.

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Psychopharmacology of the Aged

AT LEAST 20% of people 65 years of age or older suffer from psychiatric symptoms that often abate with drug treatment. Nearly a third of older patients admitted to hospital for medical-surgical care receive psychotropic drugs; the frequency for institutionalized elderly is more than 90%.

The high rate of physical illness in the upper age groups calls for comprehensive evaluation and treatment of underlying medical conditions that may cause mental symptoms before initiating any medication treatment. These physical illnesses and physiologic changes associated with aging will alter absorption, distribution, metabolism and excretion so that drug response and toxicity vary. Dosages, therefore, should begin at a lower range than for younger adults and be increased gradually to minimize side effects and identify low-dose responders.

The limited data from well-controlled clinical trials and clinical experience indicate that most psychotropic drugs used for younger adults are also effective in the elderly. Given the similar efficacy within psychotropic drug classes, the choice of a particular medication depends on its side-effect profile. Low doses of a high-potency neuroleptic drug, such as 0.5 mg to 2 mg of haloperidol, often lessen agitation and psychosis and have few anticholinergic and cardiovascular effects. Clinical trials indicate that antidepressant response rates for geriatric depression range from 30% to 80%. Serotonergic agents, such as trazodone hydrochloride or doxepin hydrochloride starting at 25 mg, appear to help agitated depressions; noradrenergic agents, such as desipramine hydrochloride or nortriptyline hydrochloride, improve retarded depressions. Two recent studies have reported pretreatment systolic orthostatic blood pressure drops of 10 mm of mercury or more to predict a favorable outcome with several tricyclic agents. Benzodiazepines are useful in treating insomnia (for instance, temazepam, 15 mg, an hour before bedtime) or daytime anxiety (lorazepam in 0.5-mg increments). Benzodiazepines with long half-lives tend to accumulate in the blood, are more likely to cause side effects and their use should be avoided.

Nonpharmacologic measures should always be attempted before using medications and often complement pharmaco-

logic approaches. Psychotherapy is an effective treatment for many forms of geriatric depression. Insomnia sometimes improves with such simple remedies as eliminating daytime napping and taking hot milk and tryptophan—0.5 to 1 gram—at bedtime.

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Changing Trends in Accusations of Child Sexual Abuse

REPORTS of child sexual abuse have risen dramatically in the past five years. In a survey recently released by the House Select Committee on Children, Families and Youth, reports of child sexual abuse nearly tripled from 1981 to 1985. This increase is probably due in large part to a heightened awareness of the problem and to mandated reporting. Whether or not the incidence of abuse has actually increased is not possible to determine at this time.

Recent sophisticated studies using retrospective reports by adults reveal important data regarding the prevalence rate and the wide range of sexually abusive activities experienced in childhood. A consistent finding throughout these studies is that the abuse was officially reported in less than 10% of cases.

In one of the more important of these studies, of 933 randomly selected adult women who were carefully interviewed, 28% experienced some kind of sexually abusive episode before age 14 years (a total of 38% before age 18). This and other studies reveal important information regarding the perpetrators of abuse and confirm some trends currently seen in intervention programs aimed at child sexual assault.

Overall, intrafamilial incestuous abuse accounts for less than half of the reported cases. Within this group almost all relatives are identified as perpetrators. Father and stepfather incest, however, accounts for less than 15% of all cases. In contrast to earlier writings, women do sexually assault children, boys more than girls, in a small but significant number of cases (around 5% of the cases of girls and 20% of cases of boys). Again in contrast to previous writings, the parent of the same sex is identified as the molester in a small but significant number of cases.

There are two major trends that present serious difficulties for a psychiatrist involved with these children. There has been a significant increase in the number of very young, preschool children brought to attention because of possible abuse. There is also an increase in the number of allegations of abuse in divorce and child-custody disputes; the latter, however, constitutes a small percentage (less than 5%) of reported cases. In both these situations a careful assessment of the validity of the accusation or suspicion is crucial to protect the child and to protect innocent adults from false accusations. Clinicians increasingly find their role as evaluator or therapist complicated (and compromised) by the need to investigate whether or not abuse occurred and, if so, the identity of the perpetrator.

There have been several attempts to develop guidelines to differentiate true from false allegations. Many clinicians working in the field, however, feel that any attempt to simplify this complex dilemma could result in a false sense of security in making this difficult distinction. Clinicians may need to acknowledge that they are not able to determine with certainty as to whether abuse has occurred and by whom, and to recommend a moderate course of action that protects both the child and the accused adult.

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Genetics of Mental Illness

EVIDENCE THAT genetic mechanisms may play a significant role in the etiology of mental illness has steadily accumulated since the beginning of the century. Although twin and adoption studies of manic-depressive illness and schizophrenia have formally established the existence of genetic factors, the actual mode of transmission is unclear, as are the means by which such genes might express themselves to create the disorders in question. The probable heterogeneity of most psychiatric disorders and their variable penetrance have also significantly confounded the design of investigative protocols and interpretation of the data produced.

One approach to this problem has been to identify possible genetic "trait markers" that may be associated in some manner with susceptibility to the disorder in question. The discovery of such markers would allow the study of persons who were genetically susceptible but who themselves had not yet experienced the formal disorder and of the mechanisms by which genes and environment could interact in additive or synergistic ways to affect the overall risk factor. In schizophrenia, genetic marker studies have focused mainly on possible associations with blood groups and with the human leucocyte antigen (HLA) system. Although most evidence would indicate no close association with any ABO blood group, many studies have found associations with various HLA markers, the most consistent finding being an association between A9 and paranoid schizophrenia. More recent reports have shown associations between schizophrenia and various class II antigens of the histocompatibility complex, suggesting that possible autoimmune mechanisms may be relevant. Other investigators have proposed poor eye tracking as a possible biologic marker for schizophrenia and reported that the transmission of both-eye tracking and schizophrenia is concordant with a single dominant gene model.

While the findings of epidemiologic studies of ABO blood types and HLA loci in affective illness have been contradictory, linkage studies of X chromosome markers such as color blindness and of HLA haplotypes have shown strong evidence of an association in a few specific pedigrees. Genetic studies of anxiety and obsessive-compulsive disorders are comparatively fewer in number, but point towards the existence of similar indices of genetic risk. Thus far, developments in recombinant DNA technology have not been widely used in

studies of the inheritance of mental illness. In one recent study, however, analysis of the segregation of restriction fragment length polymorphisms was used to locate an autosomal dominant gene strongly involved in the transmission of manic-depressive disease to the short arm of chromosome 11. The absence of such a linkage in other bipolar pedigrees indicates genetic heterogeneity.

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Predictors of Physician Performance

THE SEARCH FOR PREDICTORS of physician performance is nothing new. The predictors of whether a medical school applicant will be able to complete the work under the inevitable pressures and stress of the medical school curriculum must work pretty well since the vast majority of matriculants are successfully graduated four years later. But the predictors of whether a medical school applicant will be a "good doctor" have been harder to come by. There has been much discussion of the influence of role models and the great emphasis on science during the undergraduate medical school years and the effect of the practice habits learned in the relatively controlled and supervised environment of specialty and subspecialty training. There has been concern about whether all of this has had an adverse effect on the caring function of physicians in practice, and whether this in turn has reduced some of the affection and respect, not to mention love, that was formerly accorded doctors and the profession by their patients and the public.

Elsewhere in this issue Linn, Cope and Robbins have made a brave foray into these relatively uncharted waters by attempting to examine sociodemographic and premedical school factors that may predict graduate and postgraduate physicians' "humanistic" performance. Their studies appear to show that what happens in medical school or in postgraduate training makes very little, if any, difference in whether physicians will be more or less humanistic in their attitudes and behavior in practice situations. Rather, it is the sort of person who is admitted to medical school in the first place that is important. If that person is humanistically oriented, then these traits tend to persist in spite of what he or she may see or hear in the academic environment of the undergraduate years.

This sort of interest and this kind of a study may foreshadow a swing toward more interest in the physician-patient or humanistic aspects of health care. If this is so, then more studies such as that of Linn and co-workers will need to be done, and perhaps in time, the humanistic performance of medical school applicants will be considered as fully as important predictors of physician performance in practice as are the standard predictors of academic performance in medical school that are now used in the admissions process. If the value of these predictors can be demonstrated to the satisfaction of all concerned, it will surely be a boon to those responsible for medical school admissions who in the process select the physicians who will be the medical profession of the future.

MSMW

α_1-Antitrypsin—An Investigative Odyssey From the Benchtop to the Bedside

AS DR RESENDES POINTS OUT in this issue of the journal, our understanding of the clinical implications of protease-antiprotease homeostasis remains somewhat imperfect in the face of the recent explosion of information in this field of clinical investigation. Specifically, the saga of α_1-antitrypsin and its relevance to emphysema and other disorders has evolved over the short span of the past 25 years. The story evolves quickly from the initial recognition of the deficiency by Laurell and Eriksson[1] to a precise characterization of the molecular defect at the gene level.[2] Closely linked to this progress in experimental medicine have been the improved prospects for specific intervention in human emphysema.[3,4] As is the case in all forms of human endeavor, progress in the study of this serum protein has been matched by the generation of formidable new questions. Nonetheless, we should not be frustrated by our inability to unravel a complex problem with this single major clue. Clinical investigators cannot be other than encouraged by the quantum leap in our understanding of this disease process, coincident with the research interest in α_1-antitrypsin. It must be recalled that prior to the recovery of this (α_1-antitrypsin) piece of the emphysema puzzle, our comprehension of the pathogenesis of this disease was primitive in every respect. A fortuitous coincidence in the history of experimental medicine occurred in the early 1960s with Gross's description of a protease-induced model of emphysema and Laurell and Eriksson's "simultaneous" recognition of the elegant "experiment in nature" provided by α_1-antitrypsin deficiency. The rapid exploitation of these crucial breaks in nature's cipher provides considerable reinforcement for the joy of clinical investigation. Since those two seminal reports, the number of scientific publications in this field of clinical investigation has grown to nearly 3,000 as of April 1987. With this proliferation of published activity has come crucial insight into the cellular and molecular basis for an important human disease, as well as additional support for the crucial role of "homeostasis" between opposing physiologic processes in the preservation of normal biologic structure and function.

Although many of the hypotheses central to our present concepts of the pathogenesis of emphysema were derived directly from the lessons learned from this inherited form of the disease, the resultant investigative momentum led quickly to important clues relevant to the more common, acquired form of the disease. This initiative has led to important insight into a potential pathogenetic link between cigarette smoking and human lung disease. This investigative crossover required input from investigators in all the relevant disciplines of experimental medicine: pathology, epidemiology, biochemistry, immunology, physiology and molecular biology. In every instance, diverse experimental strategies converged to make scientific inroads into the emphysema puzzle. This progress has been limited only by the cumulative imagination of the workers in this expanding field and the available methodology. At present, it is clear that neither resource has been fully expended in the search for the complete solution to this disease process.

Nonetheless, as so well detailed in Dr Resendes's review, cracks have appeared in the buttresses supporting the "protease-antiprotease hypothesis of emphysema." Ironically, the scientific link between cigarette-induced emphysema and the form inherited with antiprotease deficiency has added complexity to the puzzle's solution. Namely, if indeed cigarette smoking induces a form of acquired functional deficiency in the lung's α_1-antitrypsin through the oxidation of a methionine residue in the inhibitor's active site, then the basis for individual variability in disease expression remains obscure. In fact, the recognition of the potential role that reactive species of oxygen may play in the pathogenesis of emphysema has resulted in the development of the "oxidant theory

of emphysema." The oxidant concept can be viewed as either a corollary or a competitor to the "conventional" protease theory of pathogenesis. The scientific interest in the biologic effects of "free radicals" of oxygen, as well as in their chemistry, has set the stage for an additional solution of this complex clinical cryptogram. Regardless of the direction in which the scientific consensus is tipped, as new leads are pursued, the interests of clinical investigation will be well served. A quarter century hence, the price of this endeavor (measured as difficult lessons of humility in science) will pale by comparison to the predictable strides made in unraveling the cipher of human disease.

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Are We Losing Ourselves Among the Trees?

IN MANY WAYS one can think of health care, and with it the medical profession, as wandering among the trees and in the underbrush of a huge forest with little or no sense of which way to turn. The trees are many—competition among physicians and with and among hospitals, government regulation within a "free" market in health care, the "bottom line," cost containment, professional liability, defensive medicine, new science, new technology, unprecedented bioethical dilemmas—to name but a few. Then, besides the trees, there is the underbrush, miserable thickets in which everything seems to get almost hopelessly tangled up—HMOs, IPAs, PPOs, DRGs, PROs—again, to name but a few. And then there are other ethical, moral and fiscal dilemmas: the balance of quality against cost, of physician advocacy of what he or she believes best or needed for a patient and the reality that there are simply not enough dollars to pay for doing everything for every patient that a well-trained physician may know how to do.

The trees and the underbrush are what we see all about us. They occupy much of the time and energy of practicing physicians and of the medical associations that represent them and their patients' interests. In many ways they deflect not only energy, but resolve and resources from what health care is all about.

But the forest is something larger than all the trees and all the underbrush. A greater reality is the people who are what health care is all about—the people who receive the care and the people who actually give the care and use their training and skills in the art and science to deliver it. Another greater reality is that 40% of the people in this nation have no health insurance at all, either public or private, and therefore can only have impaired access to care when they need it. Somewhere, somehow, there exists a right of access to needed health care. And yet another greater reality, fully as serious as the others, is that physicians and other health care providers are being diverted from placing a patient's interests first, ahead of their own or those of other parties at interest in a patient's care.

In these terms the forest itself appears as the greatest reality of all. It is telling us that what we are doing now—that is, the present approach and the present systems of health care delivery, as reflected in the trees and underbrush in the metaphor described above—is inadequate, off the mark and in the long run certain to be unacceptable. But who is listening?

Who will be the first to see the forest for what it is? Will it be the public, the people who need care and believe they have a right to it, a public that perceives itself to be underserved amidst an unprecedented plethora of superbly trained physicians and other health care personnel and in the presence of an unprecedented plethora of underutilized hospital beds and other health care resources? Or will it be a government that sees in this another and unprecedented opportunity for more bureaucratic power and control over the health and well-being of its citizens? Or could it be a profession comprised of persons whose primary incentive should be to apply its very special training and skills to give the care that is needed to patients, in a reasonably efficient system that effectively balances the needs with the resources available? Probably no group in the nation has a better view of the real forest of health care than the medical profession. Can it, or will it, step back, take account of stock as it were, and rise to see, hear and comprehend the forest that now seems so effectively obscured by the trees, not to mention the underbrush, that patently dominates so much contemporary thinking about medical practice, patient care, and indeed all of health care delivery? If this should by any chance happen it could bring about an unimagined renaissance of power and prestige for our profession.

MSMW

Perforated Diverticulitis of the Transverse Colon

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PERFORATION ACCOUNTS for about 30% to 35% of all emergency procedures done on patients with diverticulitis of the colon. Diverticulitis affects the sigmoid colon most frequently and in that location frequently presents as "left-sided appendicitis." Perforation of an inflamed sigmoid diverticulum is commonly recognized preoperatively.

Diverticulosis involves the transverse colon infrequently. Perforation of diverticulitis of the transverse colon is rare and is seldom considered in the differential diagnosis of acute abdominal pain. It lacks the more specific signs and symptoms of similar disease in the sigmoid colon. The correct diagnosis is rarely made preoperatively.

We present three cases of perforated diverticulitis of the transverse colon. The literature is reviewed to emphasize points of diagnosis and management.

Reports of Cases

Case 1

The patient, a 51-year-old woman, was admitted in late October 1983 because of nausea, vomiting, diarrhea and abdominal pain for 12 days. The pain was aching and episodic, located primarily in the right upper quadrant without radiation to the back or shoulder. She had had a similar episode 11 months before admission that resolved without treatment. Her medical history was significant for cesarean deliveries and repair of an inguinal hernia several years ago. She was treated with chlordiazepoxide for anxiety neurosis.

On physical examination she appeared anxious but in no acute distress. Her temperature was 37°C (98.6°F) and pulse 90 beats per minute. The abdomen was soft with voluntary guarding in the right upper quadrant and a question of a mass by palpation. There was no rigidity or rebound tenderness, and bowel sounds were normal. Pelvic and rectal examinations showed no abnormalities. A leukocyte count was 29,000 per μl with 67% polymorphonuclear neutrophils and 22% bands. Serum levels of bilirubin, amylase and aspartate aminotransferase (glutamic-oxaloacetic transaminase) were normal. The alkaline phosphatase was elevated to 317 IU per liter (range 29 to 93). Plain radiographs of the abdomen showed an adynamic ileus. An ultrasound study showed cholelithiasis, mildly dilated intrahepatic and extrahepatic ducts and mildly enlarged head of the pancreas. A barium enema was done on the third hospital day and showed a 20- to 30-cm area of inflammation of the transverse colon (Figure 1).

After two days of a mechanical and antibiotic preparation of the bowel, the patient was taken to the operating room. A pericolic abscess with 75 ml of pus was found near the hepatic flexure. The abscess was adjacent to the gallbladder, which was small and shrunken. Although there were several stones in the gallbladder, there was no evidence of perforation. A right hemicolectomy and cholecystectomy were done, and an intraoperative cholangiography was normal. Gross and microscopic examination of the specimen was most consistent with perforation of a solitary diverticulum 19 cm from the ileocecal valve. There was evidence of acute and chronic inflammation of the gallbladder but no evidence of perforation. Abscess cultures grew α- and nonhemolytic *Streptococcus* species and *Bacteroides* species. She was discharged on the eighth postoperative day and has been in good health since.

Case 2

The patient, a 58-year-old woman, was seen in late September 1983 because of intermittent cramping left upper quadrant pain for three days. She said she did not have nausea, diarrhea or dysuria. She noted a fever at home without any chills. She has no other medical problems. An intravenous pyelogram done in the emergency room was normal. At the time of admission she was asymptomatic and afebrile. There was slight left upper quadrant tenderness on examination without other remarkable findings. A leukocyte count was 11,200 per μl with 73% polymorphonuclear types and 2% bands. A serum amylase level was normal and a urine specimen on analysis was clear. A flexible proctosigmoidoscopy confirmed the presence of diverticula up to 40 cm. Barium enema showed extravasation of barium at the splenic flexure (Figure 2) and a few diverticula scattered throughout the sigmoid colon.

The patient underwent mechanical and antibiotic bowel preparation. An exploratory laparotomy and a left hemicolectomy with primary anastomosis were done. There was a well-confined pericolic abscess. The pathology examination confirmed the presence of a ruptured diverticulum at the splenic flexure. She was discharged nine days after the operation and has done well since.

Case 3

A 65-year-old woman was admitted early in January 1979 to the urology service to rule out acute pyelonephritis. She had presented with left lower quadrant pain and fever for one day. Her medical history showed cholecystitis and an abdominal hysterectomy. She suffered from temporal arteritis and took prednisone, 20 mg, three times a day. Throughout her early hospital stay she had temperature spikes to 39.8°C (103.6°F). Her leukocyte count was 18,200 per μl with 75% polymorphonuclear types and 20% bands. An erythrocyte sedimentation rate was elevated to 50 mm per hour (range 0 to 10). A urine specimen on analysis was clear. Serum levels of bilirubin, aspartate aminotransferase and alkaline phosphatase were normal. An amylase level was slightly elevated at 87 IU (range 5 to 75). Intravenous pyelography was normal, and proctosigmoidoscopy to 18 cm was normal. Plain radiographs of the abdomen showed extraperitoneal gas streaking along the left lower flank. A barium enema showed extravasation of barium in the left flank (Figure 3), with scattered diverticula in the sigmoid colon.

(Peck MD, Villar HV: Perforated diverticulitis of the transverse colon. West J Med 1987 Jul; 147:81-84)

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Her abdomen was explored 13 days after the initial admission and a large retroperitoneal abscess was noted at the splenic flexure. Segmental resection of 17 cm of the splenic flexure was carried out with an end-colostomy and a Hartmann pouch. Histologic examination confirmed the presence of two ruptured diverticula. The patient was discharged two weeks after the operation in good health. Her prednisone dosage was tapered to 10 mg per day. She was readmitted three months later for an uneventful takedown of her colostomy.

Discussion

With the three cases described in this article, the number of reported cases of ruptured diverticulitis of the transverse colon rises to 30 (Table 1).[1-16] The average age was 52.7 years and most (83%) were women. Two patients were on oral prednisone therapy. Only two patients had temperatures above 101.4°F (38.5°C). Leukocytosis was present in ten patients. Localization of pain was described as follows: 11 in the right lower quadrant, 1 in the left lower quadrant, 2 in the right upper quadrant and 2 in the left upper quadrant. Patients suffered from one day to five weeks before consulting their physicians.

Figure 1.—A barium enema shows a 20- to 30-cm segment of transverse colon constricted by inflammation (**arrow**). Intraoperative findings included a perforated solitary diverticulum and acute cholecystitis.

Eight patients had barium enemas done preoperatively. Three studies showed fistulas, and three showed extravasation. The other two showed short segments of colon constricted by inflammation.

The most common incorrect diagnosis was acute appendicitis, made in ten patients. Other misdiagnoses were acute cholecystitis, acute pyelonephritis, perforated colon carcinoma, colitis, infarcted appendix epiploica, inflamed retained appendiceal stump and psoas abscess.

Seven patients underwent bowel preparation before their surgical exploration. Seven patients were thought intraoperatively to have carcinoma of the colon. Operations done included resection and primary anastomosis (11), right hemicolectomy (3), resection of the diseased segment and end-colostomy (3) and exteriorization of the diseased segment (2). Solitary diverticula were present in seven patients. Postoperative complications included one episode each of thrombophlebitis and deep venous thrombosis and two deaths (from sepsis and myocardial infarction). All others recovered uneventfully.

Several points are worth emphasizing. Patients with disease in the transverse colon are generally younger than those with perforations of the sigmoid.[14] There also are slightly more women than men with the disease. One of our patients was taking prednisone for temporal arteritis. At the time of surgical intervention she was found to have a well-confined retroperitoneal abscess at the splenic flexure. This is contrary to the observation of other authors, who have noted that perforated diverticulitis of the sigmoid colon is usually followed by free perforation without formation of a walled-off abscess cavity.[16,17]

The clinical presentation of the disease lacks a specific pattern. Only two patients had fevers. The location and the severity of the abdominal pain were not helpful. Some pa-

Figure 2.—A barium enema shows extravasation at the level of the splenic flexure (**arrow**). Abdominal exploration confirmed perforation of a ruptured diverticulum.

Figure 3.—A barium enema shows extravasation of barium into the left flank (**arrows**). Exploration confirmed the presence of two ruptured diverticula at the level of the splenic flexure.

tients were acutely ill, requiring an urgent operation, and others were stable enough to undergo formal bowel preparation before a surgical procedure.

Ruptured diverticulitis of the transverse colon was most often confused with appendicitis. The correct diagnosis is difficult to make for many reasons. The location of the pain, tenderness or mass is not helpful because the transverse colon is mobile on its mesentery and can present in any quadrant of the abdomen. Moreover, because the disease occurs rarely, a clinician is unlikely to include it in the differential diagnosis. The dignostic study that is most helpful is the barium enema, which showed the abnormality in all of our patients and in an additional five patients in the literature.

The surgical treatment of perforated diverticulitis of the colon is controversial. Killingback bluntly states that "resection with anastomosis in perforated diverticulitis appears to have little or no place."[18] Other experienced clinicians use an approach based on the degree of inflammation and spread of infection.[19-21] Resection of the diseased segment and primary anastomosis were done in 14 patients with perforation at the transverse colon, and there were no subsequent complications. The approach is advocated for well-contained and localized pericolic or pelvic abscesses.[20,21] In a case of diffuse peritonitis, however, resection and an end-colostomy are more prudent. This was done in three patients without any subsequent complications.

In seven patients, the perforated diverticulum was the only one in the colon. Botsford and Curtis described only one case of solitary diverticulum at the transverse colon in a series of 100 patients with diverticulitis.[5] In series examining diverticulitis outside the sigmoid colon, however, solitary diverticula are not rare. Gouge and co-workers noted that of 14 patients with diverticulitis of the ascending colon, 4 (29%) had a solitary diverticulum.[22]

Two of our patients had diverticulosis of the sigmoid colon in addition to disease of the transverse colon. One of these two patients underwent sigmoid resection in continuity with resection of the diseased segment. Doing sigmoid resection cannot be advocated in a patient with diffuse peritonitis, but in a stable patient this is a reasonable consideration to avoid later complications of sigmoid diverticulitis.

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TABLE 1.—*Patient Characteristics of Perforated Diverticulitis of the Transverse Colon*

Patient	Age, yr	Sex	Location of Pain	Leukocyte Count/μl	Procedure	Complications	Source
1	35	♂	Upper abdomen	20,250	Exteriorization	None	Thompson and Fos, 1944[1]
2	48	♀	RLQ	...	Exteriorization	None	Lockhart-Mummary, 1949[2]
3	54	♀	RLQ	...	Resection: colostomy or anastomosis not needed	Deep venous thrombosis	Rowlands, 1951[3]
4	63	♀	RLQ	10,900	Right hemicolectomy	None	Mears et al, 1954[4]
5	...	..	...	...	Diverticulectomy and primary closure	...	Botsford and Curtis, 1961[5]
6	...	..	...	...	Cecostomy and drainage of abscess	...	Miangolarra, 1961[6]
7	...	..	...	...	Cecostomy and drainage of abscess	...	Miangolarra, 1961[6]
8	...	..	...	...	Cecostomy and drainage of abscess	...	Miangolarra, 1961[6]
9	...	..	...	...	Cecostomy and drainage of abscess	...	Miangolarra, 1961[6]
10	59	♀	RLQ	12,000	Resection and primary anastomosis	None	Kent, 1973[7]
11	30	♀	RLQ	...	Resection and primary anastomosis	None	Chughtai and Ackerman, 1974[8]
12	32	♀	RLQ	15,200	Resection and primary anastomosis	None	Chughtai and Ackerman, 1974[8]
13	39	♀	RLQ	...	Resection and primary anastomosis	None	Chughtai and Ackerman, 1974[8]
14	52	♀	RLQ	...	Ileotransverse colectomy	None	Chughtai and Ackerman, 1974[8]
15	53	♀	Generalized	...	Resection and primary anastomosis	None	Chughtai and Ackerman, 1974[8]
16	63	♀	Low abdomen	4,200	Resection and primary anastomosis	None	Chughtai and Ackerman, 1974[8]
17	51	♂	LUQ	11,000	Resection, primary anastomosis, diverting colostomy	None	Ghahremani and Olsen, 1974[9]
18	76	♂	Back, left hip	17,000	No surgical treatment	Death	Pickels et al, 1974[10]
19	39	♀	Left abdomen	...	Resection: colostomy or anastomosis not noted	Death	Vaziri, 1974[11]
20	43	♀	RLQ	...	Resection and end-colostomy	None	Wong et al, 1974[12]
21	74	♂	...	...	Resection and end-colostomy	None	Sung and O'Hara, 1978[13]
22	47	♀	RLQ	12,600	Right hemicolectomy	None	McClure and Welch, 1979[14]
23	52	♀	RLQ	9,400	Resection and primary anastomosis	None	McClure and Welch, 1979[14]
24	62	♀	RLQ	8,600	Right hemicolectomy	Superficial thrombophlebitis	McClure and Welch, 1979[14]
25	66	♀	...	...	Subtotal colectomy with ileoproctostomy	None	Rao et al, 1980[15]
26	...	...	...	...			Sakai et al, 1981[16]
27	...	...	...	...			Sakai et al, 1981[16]
28	51	♀	RUQ	29,000	Resection and primary anastomosis	None	This study
29	58	♀	LUQ	11,200	Resection and primary anastomosis	None	This study
30	65	♀	LLQ	18,200	Resection and end-colostomy	None	This study

LLQ=left lower quadrant, LUQ=left upper quadrant, RLQ=right lower quadrant, RUQ=right upper quadrant

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Hematogenously Acquired *Aspergillus* Vertebral Osteomyelitis in Seemingly Immunocompetent Drug Addicts

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A BROAD VARIETY of microorganisms can cause vertebral osteomyelitis in subjects who use illicit drugs intravenously.[1] *Aspergillus* species are ubiquitous in nature and have been found in as many as 25% of heroin samples,[2] yet they have been implicated in only one previously reported case of spinal infection, perhaps because they generally cause invasive disease only in persons who have defects in their phagocytic cells. We now report the occurrence of *Aspergillus* vertebral osteomyelitis in two drug abusers whose polymorphonuclear leukocytes (PMNs) were studied and found to be normal both in number and in function. Both patients recovered uneventfully after combined medical and surgical therapy.

Reports of Cases

Case 1

The patient, a previously healthy 34-year-old black male house painter, was admitted to hospital for low back pain of two months' duration. He had used heroin intravenously for ten years but said he was not an alcoholic, did not have diabetes mellitus or a history of hepatitis, was not homosexual and had not had trauma or a back operation. The physical examination showed no abnormalities except for localized mid-lumbar back pain. Complete blood counts, blood chemistry levels and results of liver function tests were normal. Roentgenograms showed narrowing of the L1-2 interspace with minimal destruction of bone. On histologic examination of specimens obtained at open biopsy and a laminectomy, there was invasion of bone by fungi, which proved to be *Aspergillus fumigatus* by culture. Antibodies to the human immunodeficiency virus (HIV) were not detected. Delayed-type hypersensitivity skin testing showed reactivity to *Candida* and *Trichophyton* antigens. Lymphocytes proliferated normally in response to phytohemagglutinin, concanavalin A and pokeweed mitogen. The patient's PMNs showed a normal capacity both to ingest and to kill a reference bacterial strain.[3] He recovered after receiving 2,000 mg of amphotericin B during a 60-day treatment period.

ABBREVIATIONS USED IN TEXT
HIV = human immunodeficiency virus
PMN = polymorphonuclear leukocyte

Case 2

An otherwise healthy 30-year-old black man was admitted to evaluate thoracic back pain of three months' duration. He had a ten-year history of intravenous heroin abuse but no other predisposing conditions. On physical examination there was focal tenderness over the sixth thoracic vertebra. Complete blood counts, blood chemistry levels and results of liver function tests were normal. A roentgenogram of the chest disclosed no parenchymal or pleural disease. The T6-7 interspace was narrowed and the contiguous vertebral bodies were extensively eroded. Material obtained by a Craig needle biopsy grew *Aspergillus terreus.* The patient received 2,000 mg of amphotericin B during the next two months. Because of intermittent fevers and a progressive kyphotic deformity, he underwent laminectomy with rib graft arthrodesis. Histologic examination showed persistence of fungal elements, but cultures were negative. Six months later the patient was in good health with only occasional mild back pain. At that time, an enzyme-linked immunosorbent assay for antibodies to HIV was negative; lymphocyte proliferative responses to phytohemagglutinin, concanavalin A, pokeweed mitogen, *Candida,* diphtheria toxoid and tetanus toxoid were all normal, and his PMNs phagocytosed and killed the reference bacterial strain normally.

Discussion

In adults, invasive *Aspergillus* infection is generally thought to occur in a clinical setting that is characterized by severe compromise of phagocytic function.[4,5] This clinical association, supported by various laboratory observations, has implicated mononuclear and polymorphonuclear phagocytic function as being critical to host defenses against this organism. Mononuclear phagocytes serve to kill the fungus in its conidial stage, while PMNs provide the major defense against mycelia; invasive infection generally occurs only when both lines of phagocytic cells are damaged.[6] Humoral and cell-mediated immunity seems to play little, if any, role in resistance. Thus, patients with hypogammaglobulinemia[4] or

(Brown DL, Musher DM, Taffet GE: Hematogenously acquired *Aspergillus* vertebral osteomyelitis in seemingly immunocompetent drug addicts. West J Med 1987 Jul; 147:84-85)

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TABLE 1.—*Previously Reported Cases of Hematogenously Acquired* Aspergillus *Vertebral Osteomyelitis in Adults*

Case	Author	Age, yr	Sex	Aspergillus Species	Underlying Disease or Causes of Immunosuppression	Treatment	Outcome
1	Grossman, 1975[10]	44	♂	*fumigatus*	Renal transplant; long-term use of prednisone, azathioprine	Amphotericin B	Died of myocardial infarction
2	Ingwer et al, 1978[11]	49	♂	*fumigatus*	Renal transplant; long-term use of methylprednisolone, azathioprine	Debridement, amphotericin B	Died of gastrointestinal hemorrhage
3	Tack et al, 1982[12]	61	♀	*fumigatus*	Idiopathic thrombocytopenic purpura; long-term use of prednisone	Debridement, amphotericin B	Died of staphylococcal sepsis
4	Byrd et al, 1982[13]	52	♀	Unknown	Renal transplant; long-term use of prednisone, azathioprine	Debridement, amphotericin B	Died of *Pseudomonas* sepsis
5	Seligsohn et al, 1977[14]	42	♀	*terreus*	Alcoholism, cirrhosis, intravenous drug abuse	Amphotericin B	Recovered
6	Roselle and Baird, 1979[15]	54	♂	*flavipes*	Cerebral edema; dexamethasone use in recent past	Debridement, amphotericin B	Recovered
7	McKee et al, 1984[16]	22	♂	*fumigatus*	Glucose 6-phosphate-dehydrogenase deficiency	Debridement, amphotericin B	Recovered
8	This report	34	♂	*fumigatus*	Intravenous drug abuse	Debridement, amphotericin B	Recovered
9	This report	30	♂	*terreus*	Intravenous drug abuse	Debridement, amphotericin B	Recovered

the acquired immunodeficiency syndrome[7] are not at increased risk for the development of these infections.

Review of the seven previously reported cases of hematogenously acquired *Aspergillus* vertebral osteomyelitis (Table 1) indicates that while four patients had clear evidence for suppression of PMN function (cases 1 to 4), three others had only potential or mild abnormalities in this regard (cases 5 to 7). There was no evidence of impaired function of either phagocytic cell line in the cases reported herein. Normal PMN phagocytosis and killing of a reference bacterial strain showed that the complex biochemical processes that modulate ingestion and oxygen radical formation were intact. Although the microbicidal activity of macrophages was not directly studied, these cells supported normal lymphocyte proliferative responses indicating that they were able to recognize, ingest, process and present antigen appropriately. Assays of phagocytosis and killing of *Aspergillus* were not done. Although an apparently specific defect in phagocytic killing of *Aspergillus* has been reported by Italian investigators,[8,9] this has been manifest early in life with recurrent *Aspergillus* infections and a poor response to therapy.

The elevations of immunoglobulin M and circulating immune complexes and the false-positive VDRL and rheumatoid factor tests that are commonly found in addicts suggest that some degree of immunologic abnormality results from parenteral heroin abuse.[17] Defective phagocytic function, however, has not, to our knowledge, been previously shown. Thus, the occurrence of *Aspergillus* vertebral osteomyelitis in our patients, neither of whom had recognizable immunologic defects, indicates that this infection may occur as a result of transient suppression of phagocytic function or in the absence of detectable immunologic dysfunction.

It is of special interest to note that patients who lack obvious evidence for immune suppression usually do recover when treated with standard medical and surgical therapy (Table 1, cases 5 through 9). A recent report has suggested that pulmonary infections in nonimmunocompromised patients[18] may be cured by the prompt institution of treatment with amphotericin B.[18] The uniformly poor outcome in disseminated *Aspergillus* infections thus seems to be confined to patients who have more profound and persistent defects in immune function; these persons are expected to respond poorly to treatment and to die of the infection or of complications of their underlying illnesses. It is to this group of patients that new approaches to treatment should be directed.

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Correspondence

Preventive Care Screening for Adolescents—What About Substance Abuse Screening?

TO THE EDITOR: The article "Screening in Preventive Care for Adolescents" by Braveman and Toomey in the April issue[1] noted that the major health risks for US adolescents are behavioral. They state that as many as 76% of adolescent deaths in the United States are caused by accidents, homicide and suicide. While we appreciate that they are aware of this phenomenon, it is quite apparent that the screening schedule which is offered as an outline in the text and their discussions related to behavioral history taking and substance abuse are woefully inadequate. In fact, there is no mention on the screening schedule outline of substance abuse or any behavioral questions. There are also no references in the text to lead interested physicians in the direction of how to adequately screen for teenage substance abuse, which is so frequently involved in teenage depression, suicide and accidents. We find this paradoxical, given the authors' statement that "a rational approach to health screening for adolescents would systematically address their most significant risks for morbidity and mortality, not only in youth but also in adulthood."

We would recommend for those primary care physicians interested in focusing on the major causes of morbidity and mortality in adolescents—substance abuse and behavioral disorders—that these areas be noted separately and numbered accordingly under the area of history. Further, for those interested in pursuing practical expertise in chemical dependency, the book *Drugs, Drinking and Adolescents*[2] by Dr Donald Ian MacDonald should be read cover to cover. There are sections in Dr MacDonald's book that deal more directly with diagnosis and intervention as well as other sections on dealing with parent-support groups and school systems.

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Dental Professionals and HIV Infection

TO THE EDITOR: In "Absence of HIV Antibody Among Dental Professionals Exposed to Infected Patients" by Flynn and co-workers in the April issue,[1] data were presented to show that dental professionals are at minimal risk of occupationally acquired human immunodeficiency virus (HIV) infection. It is paramount to realize that this report merely adds an additional 255 seronegative dental professionals at risk of infection to 1,078 previously reported but unacknowledged by the authors.[2-4]

That the authors failed to cite any of the existing published reports on this important topic is distressing since it is vital to present all scientific reports in the perspective of previous published work on the same subject. Although neither substantially new nor unique, this article does serve to corroborate the reports published by others, further defines the minimal risk of occupational HIV infection to dentists and their employees and reinforces the need for dental professionals at large to rigorously exercise infection control procedures since only a relatively small proportion of the members of this health care provider group has yet been evaluated.

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Hypomagnesemia

TO THE EDITOR: "When you hear hoofbeats, you should think of horses, not zebras!" How often have clinical teachers explained to their students and house officers to remember that, indeed, common things occur commonly. Similarly when clinicians detect hypomagnesemia in their patients, they should first consider the possibility of magnesium deficiency and not think of reasons why the hypomagnesemia is insignificant.

Magnesium is the second most abundant intracellular cation and is an essential cofactor in all biological systems involving bioenergetics. To our knowledge, all well-controlled experimental and clinical studies of magnesium depletion, without exception, have been accompanied by hypomagnesemia. While there are times when magnesium deficiency occurs in the presence of a normal serum magnesium level, it is an exception. Hypomagnesemia, in the presence of a normal serum protein concentration, is indicative of magnesium depletion and should be treated.

Clinical magnesium deficiency is a relatively frequent occurrence among in-hospital patients with estimates of hypomagnesemia ranging from 6.9% to 11%.[1,2] Concurrent hypomagnesemia among hypokalemic patients has been estimated to be between 38% and 42%.[3,4] Hypomagnesemia has also been reported to occur in 23% of hyponatremic patients and 29% of hypophosphatemic patients.[5] Patients with commonly occurring illnesses requiring hospital admission are at risk for magnesium depletion and hypomagnesemia: alcoholic patients with or without cirrhosis; patients with congestive heart failure or hypertension who are receiving diuretics, especially the potent loop blockers; patients with chronic obstructive pulmonary disease; patients on prolonged intravenous

therapy without adequate magnesium replacement, and those with upper or lower gastrointestinal tract fluid losses.

Since clinical magnesium deficiency and hypomagnesemia occur in a wide variety of human diseases, we recommend that serum magnesium be measured routinely in all patients in whom serum electrolyte determinations are necessary for clinical management.[6] As with the detection of hypokalemia that leads to potassium administration, detecting hypomagnesemia should entrain a therapeutic response: the administration of magnesium.

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The California Alpha-Fetoprotein Screening Program Defended

To the Editor: I read with interest the comments of Drs Stillman and Hoffman,[1] Lasnover[2] and Priver[3] concerning the California Alpha Fetoprotein Screening program. I would like to extend the invitation for any participating physician to write us directly, as Dr Priver did, to give us their constructive criticisms and suggestions. We are pleased that, in a program of this scope which involves more than 6,000 physicians and has tested almost 200,000 women, there have been so few criticisms. This is not to say the program cannot be improved, and we are implementing improvements as circumstances permit.

As to the content, certain observations need to be made. The problem of "AFP anxiety" was of concern to the state in developing our test procedures. We have reviewed the several studies on this question, including the study by Faden and co-workers.[4] These studies all come to the conclusion that the benefits of the test outweigh the acknowledged harm caused to some sensitive and overly anxious patients. In the absence of a state program, there would still be an obligation to inform and test your pregnant patients, with the attendant anxiety. While we empathize with the physicians and the women, it is the inescapable advance of technology, not the program, that inevitably generates anxiety. Our task is to see that technology is appropriately and skillfully applied so as to maximize its benefits and minimize its unavoidable negative effects. Studies show the fastest way to relieve anxiety is to expedite the follow-up tests and reports, which we attempt to do. In addition, we are expanding and revising our patient booklet, in response to physicians' input.

The feeling that a neural tube disorder is far less likely to occur than many other anomalies is true if you consider treatable defects such as congenital hip, cleft palate or extra digits. Among serious birth defects, however, it is exceeded in frequency only by congenital heart defects and the Down's syndrome. In spite of the fact that with early identification and aggressive treatment—less than 20% are mentally retarded and much rehabilitative surgical treatment can be done—it remains a serious handicapping disorder. The evidence is clear that this is an important public health problem. Moreover, in addition to detecting neural tube disorder, the test has led to the identification of chromosomal disorders, ventral wall defects, molar pregnancies and a variety of treatable disorders and pregnancy complications.

The requirement that a test be "100% reliable" would seem to be a difficult, if not impossible, criterion for any laboratory or clinical procedure. The comprehensive sequence of tests used in the California Alpha Fetoprotein Screening program is highly reliable whenever it designates an abnormality—that is, a case of neural tube defect or chromosomal disorder. It can be considered unreliable only in the sense it will misclassify 20% of open neural tube defects and 80% of chromosomal defects as normal.

The policy as to informing patients of positive results is based on legal obligations to the women who use our services and experience. However, it has always been the policy and intention to work through a woman's physician, using the letter as a backup. We are currently investigating a way to reduce these letters to cases where follow-up is difficult. Physicians are notified first, and the patient letter is delayed several days to give time for a personal contact by the physician, who has the rapport to alleviate anxiety. As a result of input such as Dr Priver's letter, this policy has been improved. In addition, we will shortly be making available to physicians a booklet to be used with patients whose blood tests are positive to help reduce anxiety. The patient's name and address are used for billing, so insertion of the physician's name in place of the patient's name will result in unnecessary inconvenience to all concerned.

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Topics in Primary Care Medicine

Treating Somatizing Patients

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Somatization is generally defined as the experience and expression of psychosocial distress or emotional problems primarily through physical symptoms. Somatization is a common, costly and frequently unrecognized condition in primary care. It is estimated that 25% to 75% of patient visits to primary care physicians are primarily due to psychosocial distress presenting as somatic complaints. Furthermore, nearly half of patients with mental illness are treated exclusively in primary care settings, usually for vague constitutional symptoms, unexplained regional pain or requests for checkups. Many somatizing patients are treated symptomatically without accurate recognition of their underlying psychosocial problems. These patients are disproportionately high users of telephone contacts, office visits, diagnostic procedures, hospital admissions and operations. Complications of chronic somatization include decreased functional status, chronic illness behavior and iatrogenic illness.

Simply ruling out organic disease is rarely a useful strategy in diagnosing somatizing patients. Some of them have coexisting organic disease and symptoms that are either unrelated to the disease, out of proportion to objective findings or refractory despite objective response to treatment. In patients without a recognizable organic disease, repetitive or extensive diagnostic testing rarely excludes organic disease with absolute certainty and may yield false-positive results prompting further testing. To make matters worse, somatizing patients may increase the urgency of their symptoms in response to a physician's uncertainty or concern, prompting physicians into actions that in retrospect might seem hasty or ill-advised. Thus, somatizing patients are more likely to suffer morbidity from repeated or invasive, but nondiagnostic, evaluations than from undiagnosed organic disease.

The diagnosis of somatization is based more on positive identification of psychosocial distress or a psychiatric disorder associated with somatization than on the absence of a recognizable organic disease. The most effective diagnostic tool in this regard is the interview. When allowed to talk, most patients describe their symptoms in the context of important events, circumstances and other people. Psychosocial information, when volunteered by a patient in this way, is more likely to be relevant and accurate than that obtained by direct questioning. Personality style, sensitivity to somatic and emotional stimuli, sociocultural factors, ongoing psychosocial stresses and previous experiences with illness and medical care can all influence the formation and maintenance of somatizing symptoms. Questions about attributions ("What do you think is causing your problem?") and expectations ("How did you hope I could help?") often help patients reveal sensitive concerns. Attention to nonverbal behavior is also important, and commenting on a patient's expression or affect can be a positive turning point in the interview.

The interview is also critical in identifying psychiatric disorders associated with somatization. Anxiety and depression are common psychiatric disorders in primary care and are characterized by mood disturbance and somatic symptoms. Patients (and their physicians) may focus exclusively on the somatic symptoms of these disorders and fail to recognize the mood disturbance or its diagnostic importance. This occurs most often in patients with panic disorder (a type of anxiety characterized by episodic "fight-or-flight" symptoms) or major depression "masked" by atypical somatic complaints. Somatoform disorders are a different group of psychiatric disorders in which somatic complaints are the major diagnostic feature. The four most important somatoform disorders are somatization disorder, conversion disorder, hypochondriasis and psychogenic pain. Patients with somatization disorder have multiple symptoms in several organ systems starting at an early age. Patients with conversion disorder have fewer symptoms that conform to their own idiosyncratic ideas about illness. Hypochondriacal patients are convinced that they have one or more serious diseases and are preoccupied with their bodily functions. Patients with psychogenic pain have symptoms limited to pain that do not fit into the other diagnostic categories. The clinical features of the four somatoform disorders overlap with each other and with those of anxiety and depression, and the usefulness of these diagnostic categories in the primary care setting remains to be proved. Distinguishing among the various somatoform disorders is a relatively less important task for primary care physicians than detecting anxiety and depression, which are more common and more likely to respond to drug treatment.

(Gordon GH: Treating somatizing patients. West J Med 1987 Jul; 147:88-91)

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Treatment Strategies

The therapeutic approach to somatizing patients depends in part on the chronicity of the condition. Young patients with no underlying medical or psychiatric illnesses who have somatization when there is a clear psychosocial stress can often be reassured successfully after an appropriate evaluation and explanation of their symptoms. Patients with chronic somatization, on the other hand, often refuse to explore the life context of the illness and blame previous physicians for failing to find diseases. These patients will probably not accept reassurance, and one or more of the strategies described below should be used.

Legitimize Symptoms

Somatization is rarely a conscious process, and most patients with chronic somatization interpret a psychological explanation for their symptoms as an accusation of lying or imagining them. Convincing patients that the physician believes in their symptoms and that he or she will not try to "talk them out of it" is critical. This is most easily done by paying close attention to the patient's spontaneous description of the symptoms and by doing a careful, pertinent physical examination. This respect gives the patient "permission," but not necessarily encouragement, to have the symptoms despite a negative evaluation.

Diagnostic restraint is particularly important in treating somatizing patients. The extent of the search for organic disease must be tailored to each patient and is a matter of clinical judgment. Somatic symptoms in these patients should be evaluated thoroughly in a stepwise manner, starting with a careful physical examination and simple or routine diagnostic testing where appropriate until a reasonable level of diagnostic certainty exists. Patients must then be carefully and regularly monitored for the development of new or evolving symptoms or signs suggesting an organic basis for their complaints.

Diagnostic labels are of critical importance. Many somatizing patients receive diagnoses that cannot be ruled in or out conclusively by objective methods, leading to misconceptions about the nature of the illness. When patients already have diagnostic labels for their symptoms, the meanings that they attach to the labels should be clarified. Some patients find psychophysiologic explanations for symptoms such as hyperventilation or tension headache to be useful, and these explanations may increase their acceptance of psychotropic medication if it is indicated. Such explanations should initially be provided in general terms because some patients will become preoccupied with irrelevant details. Often the best approach is to share uncertainty with the patient about the origins of the symptoms, while expressing concern and commitment in providing care. Neutral, descriptive diagnostic labels such as "atypical left chest pain" or "multiple complaints following traumatic injury" inform both patients and physicians of the important characteristics of the symptoms without prompting unwarranted assumptions.

Reformulate Treatment Goals

Physicians treating somatizing patients must alter their expectations about the goals and success of treatment. The usual therapeutic goals of curing, improving or at least explaining symptoms to patients in pathophysiologic terms are rarely tenable. Instead, treatment goals should be focused on modifying illness behavior and functional status. Reasonable initial goals might be to decrease the urgency or frequency of unscheduled visits and telephone calls, or to decrease the number and duration of workups or hospital admissions. Later goals might include helping patients feel more in control of themselves and their symptoms, improving their social or occupational function or helping them find ways to communicate without using symptoms. Therapeutic gains may be delayed, transient or difficult to recognize.

Treating somatizing patients also requires modification of the usual pace and activity of treatment. Successful treatment depends on establishing a caring, respectful relationship focused on understanding symptoms and promoting healthy behaviors. Establishing a therapeutic relationship may take time, and the work of building and maintaining the relationship must be shared. Physicians should avoid taking full responsibility for defining and achieving treatment goals and instead should share these tasks with the patient. This consensual approach keeps patients invested in their treatment and keeps physicians from feeling overly responsible for their patients' discouragement, anger or neediness.

Schedule Regular Visits

Patients with chronic somatization should initially be seen for at least 20 to 30 minutes every two to four weeks, even if their symptoms are stable. There are three major reasons for scheduling regular appointments. First, it removes the dependency of visits on new or worsening symptoms and avoids rewarding such developments with earlier visits. Second, it decreases a patient's fear of abandonment by the physician, which is a major cause of doctor-shopping. Finally, it permits regular evaluation of the patient's complaints so that no objective findings go undetected. Once a therapeutic relationship is established, the frequency of visits can be adjusted to the patient's current needs.

During these visits, further information should be sought about the patient's symptoms, life setting of the onset of illness and previous experiences with medical care. The physician should follow the patient's leads and avoid focusing on symptoms or medications alone. Patients who are able to develop trust and rapport in this environment will go on to discuss troubles other than their somatic complaints. When confronted with this fact, however, they may quickly return to their symptoms. Some patients will become angry or impatient when an aggressive approach to their symptoms is not forthcoming, and they do not return. These patients cannot tolerate a consistent therapeutic relationship and prefer to receive episodic care.

Address Areas of Conflict Explicitly

Common areas of conflict in a physician-patient relationship include the nature of the illness, the goals, methods or conditions of treatment and the nature of the therapeutic relationship. When physicians and patients disagree in one or more of these areas but allow treatment to proceed without a frank discussion, they both become angry and frustrated. To manage physician-patient conflict effectively, areas of agreement and disagreement must be identified and expressed explicitly. (Imagine, for example, that a physician is seeing a patient who has chronic back pain and no objective findings on thorough evaluation. The history reveals several psychosocial stressors, but the patient angrily denies their potential relationship to his or her symptoms. When the physician asks

how he or she can help, the patient states that only an operation will help. The physician might tell this patient that the condition is complex and that all aspects of the back pain, including psychosocial factors, should be explored before an operation is recommended). Next, physicians and patients must be explicit about their capabilities and limitations. (For example, the physician might find that the patient is willing to undergo invasive medical procedures but is unwilling to explore any psychosocial aspects of his or her pain. The physician, on the other hand, might be unwilling to recommend a surgical procedure without knowing more about the patient.) Once these "cards are on the table," physicians and patients must negotiate or compromise to reach a mutual agreement if they want to continue the relationship. Common negotiating techniques include making an initial concession, offering a sample treatment, sharing control of a disputed point or bringing in a third party such as a consultant. (For example, the physician might propose to the patient with back pain that visits be made on a regular basis to discuss the pain, for examinations and to provide analgesics before considering a surgical consultation. The patient, in turn, must not seek medications or surgical opinions except through that physician and must agree that no procedures will be done until the physician has had a chance to review the patient's records and to get to know him or her better.)

Manage Troublesome Emotions

Sometimes the emotional themes elaborated by somatizing patients are the most troublesome aspect of their care. It is useful to recognize these themes and to have strategies for dealing with them. Three themes are common in somatizing patients and difficult for physicians.

Suffering. Some patients describe their premorbid lives as rewarding but burdensome, with achievements gained only through adversity and self-sacrifice. Their achievements tend to focus on providing for others, such as spouses and children. These patients often become chronically ill just as their tasks end and their goals are reached. This might occur at retirement or when the children move away from home. Another group of suffering patients simply gives life-long histories of defeats, bad luck and accidents. Somatizing symptoms in suffering patients may replace feelings of guilt, resentment or low self-esteem. Sometimes overtly appreciating the burden these patients carry is therapeutic: "Mrs Smith, I just don't know how you can volunteer at the garden club every week with your bowels the way they are." A physician might even consider making the treatment itself a burdensome sacrifice: "I'm reluctant to give you this laxative because it can cause gas, but I'd like you to try it." Appealing to the willingness of these patients to do things for others rather than for themselves may be useful in improving compliance.

Hostility. Some patients experience illness as a loss of control over themselves or their environments and react with irritation or hostility. These patients may be less hostile when allowed to control important but noncritical parts of their care such as timing medications, planning diets or monitoring physical activities. A different group of hostile patients is "pseudoindependent." These patients have strong unmet dependency needs that they deny by rejecting the patient role and asserting that they can care for themselves under any circumstances. Settings of enforced dependency such as cardiac care units may prompt these patients to sign out of the hospital against medical advice. A therapeutic approach to these patients might include downplaying the dependent aspects of patienthood and appealing to the patient's strengths and the necessity to preserve them with proper medical care. A final group of hostile patients feels short-changed by the health care system and entitled to more. It is often useful to point out to these patients that anger is a normal response to illness. By directing this anger at their providers, however, they make it difficult to receive the care they deserve.

Dependency. Overly dependent patients continually need extra attention and advice. It is important to satisfy some of these needs so that the patients do not feel abandoned. But clear limits must be set on the time spent during a visit, number of calls accepted per week and number of unscheduled visits. Dependent patients often respond well to these limits once they are confident that they will not be rejected. They may, however, test a physician's commitment to them by periodically making extra demands.

Physicians' own feelings. Physicians caring for somatizing patients may experience strong feelings of uncertainty, helplessness, hostility and guilt that they find difficult to acknowledge and share. These negative feelings may interfere, consciously or unconsciously, with patient care. Some strategies for dealing with negative feelings have already been discussed, including modifying therapeutic expectations, sharing responsibility for care with the patient, addressing areas of conflict explicitly and managing difficult emotions. Validating negative feelings by acknowledging and sharing them with colleagues is frequently useful. Finally, some physicians may find that their attitudes toward the care of somatizing patients prevent them from providing effective long-term treatment; in these cases, such commitments should be avoided.

Be Aware of Nonpharmacologic Aspects of Drugs

Some patients insist on taking medications that are not indicated, refuse appropriate medications, have many or disabling side effects or do not comply with drug regimens. These behaviors may be motivated by the psychological meanings, interpersonal communications or social consequences of taking pills. These factors can be clarified by eliciting the patient's previous experiences with medications, views about physicians and medical care and personal consequences of being ill. Some of these nonpharmacologic aspects of drug treatment can be therapeutic for somatizing patients. For example, writing a prescription is a powerful "legitimizer" of the patient's symptoms, and pills are tangible proof of the physician's care. For some particularly disorganized patients, taking medications several times a day provides stability and purpose. Finally, physicians and patients both feel that they are "doing something" when drugs are part of treatment.

Drug regimens should be simplified as much as possible for somatizing patients, and drugs for anxiety and depression should be used only when clearly indicated. Before starting any type of symptomatic drug treatment, specific target symptoms should be identified. Patients should be told that the goal of drug treatment is to make the target symptoms tolerable (not remove them completely) and to restore function (not simply provide relief). Unless these goals are discussed at the time the prescription is written, patients may resist stopping drug treatment even if the benefits have been marginal. A detailed discussion of the drug treatment of anxiety, depression and chronic pain is beyond the scope of this paper.

Use Mental Health Consultations Appropriately

A mental health consultation is clearly indicated when the diagnosis is unclear (particularly if a major psychiatric disorder is suspected); a treatment plan cannot be formulated; an ongoing treatment plan is not working; clear-cut psychiatric symptoms develop, or the patient desires psychotherapy. The consultation can also focus on the physician-patient relationship, without a patient interview. In this case, the physician might describe the patient and a characteristic interaction to the consultant to explore more effective management techniques.

Physicians should choose their mental health consultants carefully. Somatizing patients can never be "medically cleared," and the consultant must be able to work with patients who have physical complaints. The consultant must also be able to understand the primary physician's perspective of the patient and to communicate a relevant new perspective effectively. Asking the consultant a specific question may facilitate this process. Primary physicians must also be open to examination of and suggestions about their relationship with the patient. They should also have realistic expectations of the consultant's diagnostic and therapeutic capabilities. It is essential that primary physicians work closely with their mental health consultants if they are sharing the care of a somatizing patient over time. This sharing reduces the uncertainty inherent in the process of care and prevents patients from using the work of one provider to undermine that of another.

Patients should be informed if they are to be seen by a mental health consultant. Convincing them that a consultation will be beneficial may take several visits and should include a clarification of the consultant's role; it is not to prove that they are crazy or that the symptoms are "all in their head" or that they will need ongoing mental health care. Rather, it is to gather as much information as possible about a complex condition so that the primary physician and the patient together can plan the best approach to care. Finally, continuity of care with the primary physician should be reassured so that patients do not interpret the referral as an abandonment. Appointments with the primary provider should be scheduled for a time shortly after the mental health evaluation.

Conclusion

Recently, by using a randomized crossover design, elements of the approach outlined above were tested in a group of primary care patients with somatization disorder. The treatment intervention included a psychiatric consultation interview with a report to the primary physician confirming the diagnosis of somatization disorder and recommending regularly scheduled visits, workup of somatic complaints only when accompanied by objective abnormal physical signs and avoidance of referral to specialists unless objective signs of illness were documented. This treatment approach significantly decreased the cost of caring for somatizing patients (mostly by reducing inpatient costs) without decreasing their functional status.

The treatment of somatizing patients involves many areas of interest to primary care physicians, including interviewing and psychosocial skills, the use and interpretation of diagnostic tests, medical decision making, cost containment and patterns of health care delivery. Because primary care physicians provide most of this care, they are uniquely qualified to conduct descriptive work and clinical trials with these patients.

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Health Care Delivery

House Calls in Utah

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To learn the criteria Utah physicians use in making or not making house calls and their specialty, age and frequency of calls, a random sample of half of Utah's physicians in family practice, general practice and general medicine was surveyed. Of 225 respondents, 70% reported making house calls at an average rate of 2.6 per month. More family practitioners made house calls than did internists; older physicians made more house calls than their younger counterparts. An estimated 82% of the calls were for patients aged 65 years and older. The most frequently stated reasons for making house calls were that patients were homebound and to assess the family or home situation. Reasons given for not making house calls were inefficient use of time and lack of equipment or necessary facilities.

(Schueler MS, Harris DL, Goodenough GK, et al: House calls in Utah. West J Med 1987 Jul; 92-94)

The number of physicians making house calls has always varied. In 1978 a study showed a 75% reduction in the number of house calls made by physicians over a 15-year period.[1] In 1980 a National Health Interview Survey showed that house calls made up only 0.6% of all physician visits.[2] A 1973 survey of general practitioners and internists reported 79% of the respondents making house calls. Physicians differed, however, with 63% younger than 35 years of age and 88% between the ages of 45 and 55 making house calls.[3] In 1977, however, a study of New Jersey family practitioners reported that 82% made house calls and that there was no age-related difference among these physicians.[4] By 1980 an American Academy of Family Physicians' questionnaire showed that only 53% of the family physicians made house calls and corroborated the earlier finding that the younger physicians made fewer house calls than did their older colleagues.[5]

In studying the frequency with which physicians made house calls, the 1973 survey found that urban physicians averaged 1 house call per week and rural physicians 2.5 per week.[3] Family practitioners in the New Jersey survey in 1977 reported an average of six house calls per week.[4]

A 1985 article suggests there is a renewed interest in house calls and cites the following factors as contributing to this resurgence of interest: greater competition among physicians, the rising cost of institution-based care and the growing number of elderly in the patient population.[6] Given that the number of patients aged 75 years and older will nearly double between 1990 and the year 2000,[7] the reasons physicians have for making house calls will continue. In the *Journal of the American Geriatric Society* (1985), Burton states, "More house calls are advocated in order to provide quality care for the frail elderly and to offer them an option to institutionalization."[8]

To understand better current trends in this area of medical practice, this study was designed to determine who makes house calls, for what reasons and how frequently.

Physicians and Methods

A one-page questionnaire was designed to survey a sample of primary care physicians in Utah. Questions were asked about physician age, the type of practice, the physician's workload and the size of the community. In addition, the number of house calls made, their duration and relative physician cost were also assessed. The respondents were asked to estimate the percentage of house calls made to geriatric patients and to answer a series of questions designed to reveal the rationale for the decision to make a house call.

A random sample representing 50% of all Utah physicians in family practice, general practice and general internal medicine was sent questionnaires. Of the 384 physicians who were surveyed, 228 physicians representing about 32% of the state's total number of physicians in those specialties responded, giving a response rate of 59%. Three responses were incomplete and, hence, excluded. The remaining 225 responses were coded, keypunched and analyzed using the Statistical Package for the Social Sciences (SPSS). Nongaussian distributed variables were examined using cross-tabulations, Friedman's analysis of variance, Mann-Whitney tests and the Spearman rank-correlation test.

Results

The respondents included 109 (49%) internists, 93 (41%) family practitioners and 23 (10%) general practitioners. Of this group, most respondents did make house calls (157, or 70%), 73 family practitioners (78%), 69 internists (63%) and 15 general practitioners (65%). The difference between the frequency of family practitioners and internists making house calls was statistically significant ($P = .018$).

The number of house calls per month averaged 2.65 for those physicians making house calls (range 0 to 20, median 1.82). By specialty, general practitioners made an average of 33 house calls a month; family practitioners, 3.3 calls; internists, 1.8 calls. The physicians who make house calls were

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also asked to estimate the number of days since their last house call. The median value was 13.6 days with a range of 0 days up to 300.

Table 1 shows the size of the communities in which the respondents practiced. More physicians in the rural and suburban areas made house calls compared with the urban physicians. These differences were statistically significant ($P = .008$ for rural versus urban, $P = .01$ for suburban versus urban); the difference between the rural and the suburban physicians was not significant, however ($P = .412$).

In comparing the type of practice and the frequency of house calls, the following results were obtained: 79 physicians were in solo practice and 61 (77%) made house calls; 129 physicians were in group practice and 94 (73%) made house calls; 13 physicians were in prepaid health programs and only 2 (15%) made house calls.

The mean age of the physicians was 44.5 years (range 26 to 69). When physicians were divided into two groups, one group older than the mean and the other younger than the mean, there was a significant difference in their decisions to make house calls: For the physicians in the older group, 82% reported making house calls while only 61% of the younger group did ($P = .001$). The number of house calls made by each group was not significantly different ($P = .4215$).

TABLE 1.—*Utah Physicians Making House Calls, Based on Size of Communities*

Physicians	Size of Practice Communities: Rural (<10,000)	Suburban (10,000 to 50,000)	Urban (>50,000)
Number in each group, N = 224	31	64	129
Number making house calls (%)	26 (84)	51 (80)	79 (61)

TABLE 2.—*Workload of Utah Physicians Making House Calls*

Physicians' Workload	Physicians in Each Group, No.	Physicians Making House Calls, No. (%)
Estimate of workload	N = 222	
More than would like	49	41 (84)
About right	150	100 (67)
Less than would like	23	16 (70)
Based on reported number patient visits/wk	N = 219	
More than average	105	84 (80)
Less than average	114	68 (60)

The correlation between physician workload and the decision to make house calls was studied two ways: First, physicians were asked to describe their workload as either "more than they would like," "about right" or "less than they would like." They were then asked to estimate the number of patients they see per week. The respondents were divided into those seeing more than the average number of patients per week and those seeing fewer, based on the average number for each specialty. Table 2 shows the number of physicians making house calls in these various groups. Although a greater percentage of the physicians making house calls was in the group whose workload was "greater than they would like," it was not statistically significant ($P = .059$). There was a significant difference, however, between the number of physicians seeing more than the average number of patients and those seeing fewer patients ($P = .001$): 80% of the former group made house calls compared with 60% of the latter group.

The respondents estimated that patients aged 65 years and older make up 34% of their practice and receive 82% of the house calls. No correlation was found between the proportion of elderly patients in a physician's practice and the decision to make house calls or the number of house calls made. When asked to estimate what percentage of the house calls were scheduled, the average was 25%. The mean amount of time spent in a house call was 23.3 minutes. Of the physicians who make house calls, 74% reported charging more for a house call than for an office visit of equal duration.

Physicians were asked to assign values for the reasons influencing their decisions to make house calls. Table 3 shows the mean scores assigned to a number of factors influencing the decision. The scores range from 5 for very important to 0 for unimportant reasons.

Reasons for and against making house calls are reported in Table 4. Patient disability was clearly most often cited but assessing the home or family, patient comfort and enhancing physician-patient relationship were also important. Not surprising, the reasons most often provided for not making house calls were based on time and equipment factors.

Conclusions

Is there a renewed interest in house calls as some suggest?[6,9] Certainly, this study shows that most of the primary

TABLE 3.—*Factors Influencing Decisions to Make House Calls*

"How important are the following factors in deciding to make a house call?"	Mean score on a scale from 5 to 0*
The patient is bedbound or housebound	4.75
The patient is elderly	3.73
The patient suffers from a recent disability (MI, stroke, trauma)	3.73
The patient is suffering an acute, life-threatening event	3.49
The patient is a personal friend	3.10
The patient may need institutional care	2.95
The patient suffers from a death in the family or other crisis	2.61
The patient's home is more than 20 minutes away	2.45
You need more information about the patient	2.05
The patient is ambulatory but prefers a house call	1.24
Whether or not the patient is able to pay for the visit	0.67

MI = myocardial infarction

*5 = Very important, 0 = unimportant.

TABLE 4.—*Reasons For and Against Making House Calls*

Reasons For Making House Calls	*Number*	*Reasons Against Making House Calls*	*Number*
Patient is bedbound or disabled	105	Inefficient, time-consuming or both	121
Assess the home or family situation	37	Lack of equipment or facilities or both	99
Comfort and convenience of patient	24	Patient is able to come to clinic	47
Enhance physician-patient relationship	21	Inadequate or substandard care	43
Patient dying	18	Too expensive, not cost-effective	32

care physicians surveyed in Utah do make house calls (70%). This figure is lower than some earlier studies: in 1973 it was reported to be 79% and, in 1977, 82%.[3,4] Older physicians were again more likely to make house calls than younger physicians, a trend that was also found in 1973[3] and 1980.[5] This study also found fewer urban physicians making house calls compared with their rural and suburban counterparts, and more family practitioners were shown to make house calls than internists. In this study, the physicians who had larger workloads were the ones more likely to make house calls than were those with fewer patients, a finding not reported earlier.

In the search for the reasons why house calls are made, it was found older patients received 82% of the house calls, with the main reason cited for making house calls being related to the elderly or homebound. The average number of house calls made was 2.6 per month, a substantial reduction from the 1973 and 1977 studies, which were 1 to 2.5 per week and 6 per week, respectively.

These findings do not support claims of increased interest in making house calls. At a time, however, when the elderly population is growing rapidly, information on current house-call practices can have a number of applications: It may provide guidelines for physicians who are unsure about when to make a house call, and this information can be used to educate patients about when to request a house call. By reviewing current trends, it should be possible to forecast health care delivery needs and thus redirect the emphasis in physician education.

The 1977 survey of New Jersey family physicians asked how many house calls were made during the week before the questionnaire was completed, thus explaining the unusually high number—the survey was conducted during an outbreak of influenza. The authors suggested that the number of scheduled house calls (average 4.7) per week might represent a closer approximation of physicians' behavior, a figure that is still higher than earlier ones.

For the purpose of comparing the number of house calls made, this study is closer to the 1972 survey in terms of who was asked and the types of questions. The major difference lies in asking physicians to estimate the number of house calls on a weekly basis in 1972 rather than a monthly basis in 1986. With these points in mind, a rough comparison shows physicians making 8.6 house calls per month in 1972 and 2.6 per month in 1986, a greater than threefold reduction over a 14-year period.

The speculation recently of an increased interest in making house calls comes from Jay Siwek, MD, a faculty member at Georgetown University (Washington, DC) School of Medicine and president of the District of Columbia Academy of Family Physicians. He speculates that there is evidence of a renewed interest in house calls among physicians and the public. Because of the rising costs of institution-based care and the increasing proportion of elderly, health legislators and insurance carriers were reported to have become increasingly interested in home visits. He also suggested, in the context of increased competition among physicians, that house calls are a practice feature that appeals to many patients.[6] Objective data showing an increase in the number of house calls made as a basis for this renewed interest were not given.

Despite valid reasons for increased numbers of home visits, the latest data addressing the subject of house calls before our study showed a greater percentage of physicians made fewer house calls per month.[10] This survey, conducted by the American Medical Association in 1982, asked physicians to compare the number of house calls made per month at that time with the number made two years before: 77% reported making the same number, 8% made more and 14% reported making fewer house calls than two years earlier.

How is information on current house-call practices useful?

- Practicing physicians and students and residents in training learn that house calls are still being made by most practitioners, although relatively few in number, and that the reasons for these were that a patient is bedbound or disabled or to assess the home situation, or both—reasons that will remain valid for the foreseeable future.
- Patients need to be told that most physicians still make house calls when they are indicated. Patients should also be informed that, on the basis of this study, their ability to pay for a home visit has very little influence on whether a house call is made.
- Finally, the trend suggested by these findings—that is, showing a continued decline in the number of physicians making house calls—implies that at a time when the number of elderly patients is increasing, fewer of them are being seen at home by physicians. Thus, despite good reasons to expect more house calls, the objective data show the opposite.

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Public Health

Acute Symptoms in Persons Residing Near a Field Treated With the Soil Fumigants Methyl Bromide and Chloropicrin

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Accidental chemical releases into the air from manufacturing plants, such as occurred in Bhopal, India, and in Institute, West Virginia, have made the public increasingly aware of the health hazards associated with toxic air contaminants. Similar hazards may arise from off-gassing of fumigants from agricultural applications. This has particularly been a problem in California, where urban and suburban areas have spread into prime agricultural lands, resulting in populated areas directly abutting agricultural fields. Physicians and public health staff in such areas should be aware of such potential exposures, symptoms and the appropriate treatment and response. In this report we describe one such episode that occurred in 1984.

Field fumigation with the volatile liquids methyl bromide and chloropicrin is an agricultural practice that can cause exposure to nearby residents. Fumigants are quite toxic to humans. The most common symptoms of methyl bromide and chloropicrin exposure are listed in Table 1.[1-7] Methyl bromide is an organic halogenated aliphatic hydrocarbon with the formula CH_3Br. It is a gas at normal ambient temperatures and is readily absorbed by inhaling. Most symptoms are due to neurotoxic effects, skin irritation or (at very high doses) lung irritation.[4] Chloropicrin is an aliphatic nitro compound with the formula CCl_3NO_2. It is a gas at ambient temperatures, and symptoms are due to direct irritant effects to the skin, eyes, mucous membranes and respiratory tract.[4]

These highly effective pesticides are injected 15 cm (6 in) or more into the soil before the planting of a number of crops to control nematodes, insects, weed seeds and fungi. A common method of application is to then cover the area with a plastic tarp for at least 48 hours, burying the edges of the tarp with at least 10 cm (4 in) of firmly packed soil. The compounds volatilize in the soil, react with organic compounds in the soil and presumably dissipate slowly through the tarp and rapidly when the tarp is removed.

Episodes of illnesses in nearby communities have been reported with agricultural applications of methyl bromide and chloropicrin. Table 2 shows the details of four such episodes that were reported and recently investigated.[8,9] All four involved strawberry fields and occurred during times of little wind or of air inversion. In all episodes, the index cases were first seen in local emergency rooms. The fourth incident, which occurred in Stanislaus County in 1984, was investigated in detail by the California Department of Health Services (CDHS) and the Stanislaus County Health Department (SCHD) and is the subject of the rest of this report.

During the day of October 23, 1984, a strawberry field in Ceres, California, was fumigated preplanting with methyl bromide and chloropicrin and the field was covered by a tarp. That evening was warm, about 30°C (86°F), with an air inversion and a variable wind of 2 mph. At about 9:30 PM, the Ceres Police Department received health complaints from residents living in widening areas around the field, and at 11 PM, the SCHD and the Ceres Fire Department began going door to door to evacuate about 75 homes in the area. Later that night, symptom reports came in from a disposable diaper manufacturing plant 0.8 km (½ mi) to the west of the field, and the night shift and workers at two other nearby plants were sent home. Several other businesses were told not to open the next day, October 24. No air samples were taken at the time of the incident. The California Department of Food and Agriculture took several air samples around the area on October 24th in the late morning and early afternoon. Samples were taken by drawing a known quantity of air through sorbent tubes; these were analyzed in a local laboratory and all were negative (<1 part per billion detection level) for methyl bromide and chloropicrin, indicating that fumigants may have dispersed by late morning October 24. A sample, however, taken in the diaper plant at 11 PM on October 24 by the SCHD showed a methyl bromide level of 3 parts per million using a direct reading Drager tube method (3 ppm is the lower level of measurement for this method). Possibly there was less dispersion of the methyl bromide in the more closed environment of the plant.

Because many of the reported cases of possible exposure-related illnesses were unexpectedly distant from the site of fumigation, the CDHS and the SCHD undertook a community survey to determine the geographic extent of exposure and the nature of symptoms experienced by the community.

Methods

The locale is semirural, on the outskirts of Modesto. The field was surrounded by three distinct areas: single-family homes to the east, an industrial area to the immediate north and west with homes further north and a few homes and large fields to the south.

(Goldman LR, Mengle D, Epstein DM, et al: Acute symptoms in persons residing near a field treated with the soil fumigants methyl bromide and chloropicrin. West J Med 1987 Jul; 147:95-98)

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
SCHD = Stanislaus County Health Department

Surveys

The SCHD asked local emergency rooms to report the total number of acute illnesses that may have been attributable to the episode. The area around the fumigated field was surveyed by telephone. Homes within 3 km (2 mi) of the field and control homes further away in Ceres were selected for the survey. An attempt was made to include areas in all four directions and at distances varying from within 1 to 3 km (½ to 2 mi) from the site to assess direction and extent of symptoms, but not all areas contained homes. Cluster samples were taken of streets in the study areas, and attempts were made to contact all households on the selected streets by calling numbers listed in a reverse telephone directory. Employees of the SCHD and the CDHS were trained to administer a telephone questionnaire. All calls were made between one and three weeks after the epidemic. In all, 224 telephone numbers were called, of which there were 196 households eligible to participate. Of these, 20 (11%) were not reached and 42 (21%) refused to participate, giving a response rate among eligible households of 68%. The most common reasons given for refusing to participate were being "too busy" or, among those living further away, "we weren't involved in that." In all, 402 persons (280 adults and 122 children) from 134 households were interviewed.

A sample of residents was administered a telephone questionnaire asking about exposure and symptoms. Parents responded for their children. Questions were asked about age, race, sex, whether at home on October 23 and 24, whether absent from school or work October 23 or 24, location of schools or workplaces and the presence of possible predisposing factors for the development of symptoms, such as chronic lung disease, any other chronic illnesses and smoking. If respondents had noticed any new illnesses since October 23, they were asked about the presence and timing of 33 new symptoms. Included were symptoms known to be associated with acute exposure to methyl bromide or chloropicrin (or both). Questions concerning symptoms not known to be related to exposure were asked to help eliminate viral illnesses and to detect overreporting of symptoms.

Before analyzing the survey results, exposure syndromes for acute exposure to methyl bromide and to chloropicrin were defined (Table 3). Only symptoms occurring between October 22 and 25 were included; symptoms appearing later were not included, although some persons might have experienced delayed or secondary illnesses. Symptoms occurring in conjunction with fever were considered to have been due to infectious disease and not to fumigant exposure and were excluded. Responses were tabulated by quadrant and distance from the fumigation site. Also, responding households were mapped, and maps of affected households produced. Tabulations were produced to identify the most common symptoms among the syndromes consistent with exposure.

Results

The emergency room survey showed that 32 persons from the affected area were seen between October 23 and 25, and 3 were seen between October 25 and October 29. They had incident-related symptoms such as eye irritation, sore throat, headache, shortness of breath and cough. One 6-year-old child was hallucinating. An employee of one of the local plants was admitted for observation because of tachycardia and shortness of breath. Several workers who were called to the scene to give emergency assistance became symptomatic and were treated at a local emergency room: four fire fighters, a sanitarian, a highway patrol officer and two police officers. Blood bromide concentrations measured in these eight symptomatic persons were subsequently normal.

In the survey population, 71 adults and 23 children reported illnesses with onset after October 22 ("new" ill-

TABLE 1.—*Comparison of Use and Toxicity of Methyl Bromide and Chloropicrin*

Characteristics and Use	*Methyl Bromide*	*Chloropicrin*	*References*
Threshold limit value, ppm	5	0.1	1
Odor threshold, ppm	Practically no odor	1.1	2,3
Reported use by California agriculture, 1984, kg (lb)	3.175 million (7 million)	680,400 (1.5 million)	4
Acute toxicity			
Rat survival	6 h at 514 ppm	1 min at 340 ppm 20 min at 110 ppm	1
Human survival	No information found	10 min at 298 ppm 30 min at 119 ppm	5
Symptoms			
Acute, mild	Headache Nausea Vomiting Malaise Weakness Dyspnea Skin irritation	Odor Lacrimation Nose irritation Throat irritation Cough Nausea Vomiting Skin irritation	1,2,3,6,7
Acute, severe	Convulsions Pulmonary edema Death	Orthostatic hypotension Pulmonary edema Death	
Chronic effects	?Neurotoxicity ?Carcinogenicity ?Teratogenicity	Unknown	

ppm=parts per million

TABLE 2.—*California Episodes of Community Exposures From Methyl Bromide and Chloropicrin Soil Fumigation*

Place	Year	Weather Conditions	Index Cases, number	Comments
Los Angeles County*	1973	No wind; air inversion	3	Attack rate 53% in residents on nearest street
Ventura County†	1980	No wind	16	Fumigation stopped by the county because of illnesses
Kern County‡	1984	Air inversion	3 families	All three homes evacuated
Stanislaus County	1984	No wind; air inversion	32	Nearby plant and homes evacuated

*From Murray et al.[8] †From the California Oepartment of Health Services.[9] ‡From the *Shafter* (California) *Press*, July 4, 11 and 18, 1984.

nesses). Of these, 32 adults and 4 children in 26 households reported symptoms consistent with exposure to fumigants during October 22 through 25. For 7 adults, symptoms were possibly attributable to methyl bromide exposure and for 31 adults and 5 children, symptoms may have been attributable to chloropicrin exposure.

Symptoms were experienced in areas outside the evacuated area, which was the area within about 0.8 km (½ mi) of the field. Among adults, 30% of those surveyed who lived within 0.8 km of the field reported chloropicrin symptoms compared with 14% at 0.8 to 1.6 km (½ to 1 mi), 7.9% at 1.6 to 2.4 km (1 to 1½ mi) and 4.5% at greater than 3.2 km (2 mi) (Table 4). All 4 children with chloropicrin symptoms were in the evacuated area but, for adults, only 15 of 32 with these symptoms were in the evacuated area.

Three of the four children who had symptoms consistent with exposure lived within 0.8 km of the fumigated field, and three lived to the southeast of the field. In all four cases parents reported that children had been absent from school during their illnesses. All attended schools farther from the field than their homes were. None were reported to have chronic lung disease. There were no children living in the households interviewed in the southwest quadrant.

For adults, the greatest percentage of people with chloropicrin symptoms was in the area to the southeast of the field (Table 4). Although most symptomatic persons lived within 1 km of the site, there were also a number of them who lived up to 2.4 km (1½ mi) away from the site. Adults with possible methyl bromide symptoms were widely scattered throughout the area. Possible confounding variables such as location of work, preexisting chronic lung disease and smoking were also examined. One person, who lived 3.2 km (2 mi) to the southeast of the site and had symptoms of both methyl bromide and chloropicrin exposure, worked in a plant that was evacuated October 23. Two others, who had chloropicrin exposure symptoms only, both lived and worked in the evacuated area. People with preexisting chronic lung disease who were cigarette smokers were no more likely than others to report these symptoms.

To see which symptoms were most strongly associated with these syndromes, the symptom list was reviewed for adults with new illnesses (illnesses occurring after October 22) and with symptoms consistent with methyl bromide or chloropicrin exposure (Table 5). For those with chloropicrin syndromes, the following frequencies of reporting of symptoms were noted: eye irritation (65%), headache (48%), throat irritation (45%) and unusual odors (39%). For those with methyl bromide syndromes, the following frequencies of reporting of symptoms were noted: headache (100%), eye irritation (71%), weakness (57%), dizziness (57%), throat irritation (57%), nausea (57%), lightheadedness (43%) and cough (43%). There was considerable overlap between these groups; six of seven of those with methyl bromide symptoms also had chloropicrin symptoms. Of note is one person with both types of symptoms who also reported dysuria, a symptom not expected to be caused by either exposure.

Discussion

Methyl bromide-chloropicrin fumigation can be a hazard to surrounding communities. In the case of the Ceres incident, it is probable that unusual weather conditions or human error,

TABLE 3.—*Definition of Methyl Bromide and Chloropicrin Acute Exposure Syndromes*

Methyl Bromide Syndrome	*Chloropicrin Syndrome*
No fever, no diarrhea	No fever
At least two	*At least one*
Weakness	Eye irritation
Headache	Nose irritation
Dizziness	Noticed unusual odor
Unconsciousness	Throat irritation
Nausea	
Tremor	
Also consistent with exposure	*Also consistent with exposure*
Loss of appetite	Headache
Shortness of breath	Anxiety
Chest pain	Eye redness
Vomiting	Runny nose
	Unusual taste
	Cough
	Cough produces mucus
	Shortness of breath
	Chest pain
	Nausea
	Vomiting

TABLE 4.—*Percent of Adults With Chloropicrin Symptoms by Quadrant and Distance From the Fumigated Field*

Distance, km (mi)	Quadrant				Total
	Northeast	Southeast	Southwest	Northwest	
0 to 0.8 (0.0 to 0.5)					
n	28	12	0	0	40
(%)	(25)	(42)	...	...	(30)
0.8 to 1.6 (0.5 to 1.0)					
n	15	24	0	11	50
(%)	(0)	(21)	...	(18)	(14)
1.6 to 2.4 (1.0 to 1.5)					
n	29	27	8	27	101
(%)	(0)	(15)	(13)	(8)	(8)
>2.4 (1.5)					
n	22	15*	3	49	89
(%)	(5)	(7)	(33)	(2)	(5)
Total	94	78	11	97	280
%	(9)	(19)	(18)	(6)	(11)

*One person worked in an evacuated plant.

or both, contributed to the community exposure because past fumigations there have not caused similar episodes. Nevertheless, regulations governing fumigant application should take these possibilities into account.

In the incident investigated here, we were able to show symptoms of chloropicrin and methyl bromide exposure in neighborhoods in quadrants northeast and southeast of the fumigated field. This is consistent with the direction of the prevailing winds in the area (from the northwest). There were, however, only a few homes close to the field in the northwest and southwest so that there are not enough data to reliably estimate the rates of illnesses in these areas. Also, a plant northwest of the field and within 1 km of it was evacuated because workers experienced symptoms, indicating possible exposures in this area. Distance from the field was an important factor in the development of symptoms; nonetheless, evacuation did not succeed in moving out many of the nearby symptomatic residents.

The symptoms most commonly experienced by the exposed group were headache and eye and throat irritation. Though many of the symptoms reported were minor and nonspecific, the emergency room survey detected several more serious illnesses occurring during the same time period, including several cases with shortness of breath and a child who was hallucinating. Although chloropicrin is often added to fumigants because of ability to detect the odor, the rates for other symptoms exceeded those for the observation of unusual odor. (In this case, the chloropicrin was used as a fumigant.) No one symptom could be relied on as an index of chloropicrin exposure. For those with symptoms of possible methyl bromide exposure, headache was universal and 70% had eye irritation. It should be noted, however, that among a different group of persons (mostly symptomatic fire fighters involved with the evacuation) who were tested for methyl bromide levels, none were positive, indicating that their symptoms may have been due to chloropicrin exposure. None of the persons found in this study to have methyl bromide symptoms were tested for serum bromide concentrations as the study was done several days after the incident.

TABLE 5.—*Adults With New Symptoms Between October 22 and 25 by Presence of New Illness, Methyl Bromide Symptom Cluster and Chloropicrin Symptom Cluster, %*

Symptom	New Illness, n=71	Methyl Bromide Oct 22 to Oct 25, n=7	Chloropicrin Oct 22 to Oct 25, n=31
Fever	7	0	0
Weakness	14	57	19
Sweating	14	27	19
Loss of appetite	11	14	13
Headache	37	100	48
Lightheadedness	14	43	16
Dizziness	14	57	19
Anxiety	4	0	6
Confusion	4	14	6
Irritability	4	14	6
Unconsciousness	1	0	0
Eye irritation	28	71	65
Eye redness	6	14	10
Nose bleed	4	14	6
Runny nose	14	29	19
Nose irritation	11	29	23
Unusual odor	20	14	39
Throat irritation	23	57	45
Unusual taste	7	14	10
Cough	21	43	29
Cough produces mucus	8	29	10
Cough produces blood	1	0	3
Short of breath	14	29	19
Chest pain	11	29	19
Nausea	13	57	19
Vomiting	7	14	10
Diarrhea	8	0	13
Abdominal pain	6	0	10
Pain with urination	1	14	3
Skin irritation	8	14	10
Skin rash	0	0	0
Tingling	3	0	3
Tremor	1	0	0

A much lower percentage of children than adults were reported to have been symptomatic. This could be due to reporting or recall bias of parents for their children's symptoms compared with their own symptoms, or to a higher symptom threshold to these chemicals among children. It should be noted, however, that few children were surveyed in the areas where highest levels of symptoms among adults were found, so that estimates for children in these areas may not be reliable.

In conclusion, a community exposed to a methyl bromide and chloropicrin-fumigated field experienced high rates of airborne-irritant symptoms in the 24 hours following fumigant application. Reporting of fumigant-related symptoms dropped off sharply with distance, 30% within 1 km compared with 4.5% greater than 2 km from the field. Most symptoms were probably related to chloropicrin exposure. The fumigants were apparently applied properly and according to regulations, but atmospheric conditions (air inversion and very little wind) and high temperatures (32°C [90 °F]) probably resulted in higher ambient air concentrations than usual. These atmospheric conditions frequently occur in the California Central Valley.

Practitioners, particularly those working in emergency rooms, should be aware of the possibility of further such outbreaks occurring and the need for rapid diagnosis and calling in of county and state public health and agricultural officials. The incident highlights the need for larger buffer zones between areas where highly toxic airborne agents are being applied and residential areas. Notification of local health and emergency response agencies and the local community is imperative. There may be a need for soil pesticide scientists to develop agents that degrade more readily on site and are less likely to volatilize into the local environment.

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Sociodemographic and Premedical School Factors Related to Postgraduate Physicians' Humanistic Performance

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In an extensive survey of postgraduate physicians in two teaching hospitals (N = 141) for their humanistic attitudes, values and behavior, all ratings of physicians' humanistic performance, including physicians' own scores on self-report measures, supervising faculty, nurses and patient ratings, were modestly but significantly correlated with each other. Sex, ethnic or racial background, year of training, marital status, number of children, Alpha-Omega-Alpha membership or number of articles published were unrelated to physicians' humanistic behavior. Several measures of humanism were positively correlated with having taken more courses in the social sciences and humanities, having had more early person-centered work experience and reporting that before medical school others had confided in them or sought their advice more frequently.

(Linn LS, Cope DW, Robbins A: Sociodemographic and premedical school factors related to postgraduate physicians' humanistic performance. West J Med 1987 Jul; 147:99-103)

In a landmark 1983 decision, the American Board of Internal Medicine required all postgraduate training programs in internal medicine to assess the humanistic qualities of their residents as part of the certification process.[1] The refocusing of attention of many medical educators on the importance of humanistic physician behavior is in part due to the increasing evidence that the major academic criteria used for admission of students into medical school (college grades and scores on the Medical College Admission Test) have not been good predictors of the quality of clinical practice.[2-5] One group of medical educators headed by a surgeon recently concluded that because academic achievement correlates so poorly with the clinical performance of physicians, it probably is more important to select college students for medical school who will be superior physicians than those who will be excellent medical students.[6] They argued that this selection process should be based upon traits that are important but not easily taught or learned in medical training. Among the 12 highest ranked traits of the 87 they studied, 8 were humanistic in nature—a person of unquestionable integrity, who is forthright and intellectually honest, has sustained genuine concern for patients during their illness and convalescence, is an understanding person and is motivated by idealism, compassion and service rather than money.[6] Because previous studies of the socialization process in medical school found that cynicism among students tended to increase over the training period,[7-11] selection of more humanistic applicants is therefore of even greater importance.

As the practice of medicine evolves and changes, it is clear that people recruited and selected to be the physicians of the future must be superior in both the cognitive-academic and the affective-humanistic realms. This study focuses on the latter set of skills among trainees in two southern California postgraduate training programs in internal medicine. Our purpose was to see whether certain sociodemographic and premedical school life experiences are correlated with current assessments of humanistic performance. Our definition of humanism is multidimensional and includes values, attitudes, interpersonal skills and behaviors (verbal and nonverbal), intrapsychic self-awareness and the effect a physician has on the feelings of others. Specific attributes of these dimensions include integrity, respect, compassion, empathy, patient-centeredness and an attitude that is caring, respectful and sensitive to others. Our measures of humanism will include self-reported measures and the ratings of supervising physicians, nurses and outpatients.

Physicians and Methods

Sample and Design

Two physician populations were asked to participate in the study by completing a battery of self-reported measures. The first population consisted of all 117 internal medicine house staff and faculty who had seen outpatients in an ambulatory care center in a teaching hospital (hospital A) during the 1984-1985 academic year. A total of 95 completed questionnaires was returned, for a response rate of 81%. The second population consisted of all 49 internal medicine house staff in training at a second teaching hospital (hospital B). Completed questionnaires were returned by 46, for a response rate of 94%. Thus, the total sample consisted of 141 physicians, 90% of those asked to participate. Of the respondents, 38% were interns, 23% were second-year postgraduates, 29% third-year postgraduates and 10% were faculty. Of the group, 58% were unmarried, 87% had no children, 28% were women and 27% were from a racial minority group.

In both training programs, the training director sent all

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This research was supported by a grant from the Borun Foundation and the UCLA Committee for Humanistic Care.

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ABBREVIATIONS USED IN TEXT

AOA = Alpha Omega Alpha
HUMPTS = Humanistic Toward Patients Scale
HUMSTF = Humanistic Toward Staff Scale

house staff and faculty a letter describing the project and requesting participation. In hospital A, questionnaires were distributed by two medical students who contacted each potential respondent. In hospital B, contact was made by a postgraduate fellow or staff from the office of the training director.

Self-report Measures

After an extensive review of the literature, five self-report measures were selected for administration: the Hogan Empathy Scale,[12] the Physician Humanism Scale,[13] the Survey of Interpersonal Values (the benevolence subscale),[14] the Affective Communication Test[15] and the Care-Cure Orientation Index.[16,17] All scales met conventional standards of reliability and validity that have been described in greater detail elsewhere.[18] In the present study, the five instruments have been used together as a battery consisting of 119 items, with a mean score of 249, a standard deviation of 30 and a range of 173 to 326. The Hogan Scale is a measure of empathy from the California Psychological Inventory. The Physician Humanism Scale is a measure of physicians' attitudes toward social, medical and psychiatric issues. The benevolence subscale of the Survey of Interpersonal Values measures physicians' willingness to do things for or share with others and to be generous and help the unfortunate. The Affective Communication Test measures nonverbal expressiveness, and the Care-Cure index measures the degree to which physicians value caring for patients over curing them. This battery of measures does not require extensive medical training or expertise and can be completed by premed, medical school, postgraduate or practicing physician populations.

Faculty, Nurse and Patient Ratings

Faculty, nurse and patient ratings were obtained only on physicians in hospital A. In March and April 1985, 14 nonphysician staff members of a medical ambulatory care center independently evaluated each house staff and faculty physician currently seeing patients on two criteria: a seven-item Humanistic Toward Patients Scale (HUMPTS) and a six-item Humanistic Toward Staff Scale (HUMSTF). These scales had Cronbach's α-reliability coefficients of .92 and .90, respectively.[19]

In July through September 1985, patient satisfaction ratings were gathered from four new patients and three continuing patients seen consecutively by each house-staff and faculty physician in the same ambulatory care center in hospital A where the nonphysician ratings were obtained. The Art of Care Patient Satisfaction Scale consisted of nine items measured on a five-point Likert scale, had an α-reliability coefficient of .85 and has been described in detail elsewhere.[20,21]

Faculty evaluations of house-staff performance on inpatient ward rotations were collected for the period of July 1984 to September 1985. An average of ten evaluations per physician was available. This evaluation form consisted of 18 items, 8 measuring the technical quality of the physician's performance, 8 measuring humanistic performance and 2 items measuring general qualities. An overall rating of clinical competency was also assessed. All qualities and behaviors were assessed on a nine-point continuum from outstanding to unsatisfactory. The Humanism Scale consisted of the following eight items: cooperation with medical colleagues, cooperation with paramedical staff, physician-patient relationship, rendering of comfort and empathy, involvement of patients in decisions, consideration of patients' concerns, ability to put patients at ease and render comfort and integrity to admit errors. Cronbach's α-reliability coefficient for this scale was .97. We will present data for this humanism scale and for faculty physicians' ratings of overall clinical competence.

Demographic and Premedical School Experiences

All respondents were asked to indicate their race, sex, marital status, whether or not they had children and number of siblings. In the educational realm, they were asked whether or not they belonged to Alpha Omega Alpha (AOA), how many articles they had published in a scientific or scholarly journal, their level of training and the number of social science and humanities courses taken in college. They were also asked whether their parents were divorced and whether any member of their immediate families had died.

Respondents were also asked to indicate any experience they had had before medical school working in a physician's office, hospital or clinic, doing child care or working in a children's camp, helping the disadvantaged, teaching, working in a nursing home or with the elderly, working for a political party or in a political or social action movement.

In addition, physicians were asked to indicate how often as a child they were able to accurately anticipate what their parents were going to say before they said it, how often they were able to accurately complete sentences begun by their close friends or family and how often before going to medical school their friends confided in them about personal problems or turned to them for advice.

Hypotheses

Four general hypotheses were tested:

- There is no significant relationship between humanistic physician attitudes and behaviors and their demographic characteristics.
- Physicians with person-centered premedical school work or volunteer experience will have significantly higher humanism scores or ratings than physicians without such early work experience.
- Physicians who took more courses in the social sciences and humanities as undergraduates will have significantly higher humanism scores or ratings than physicians with less course work of that kind.
- Physicians with premedical school histories of being more empathic or having been used as a source of advice and confidence more frequently by their friends will have significantly higher humanism scores or ratings.

Results

Looking first at the correlations among measures of humanistic physician performance (and overall ratings of clinical competence), Table 1 clearly shows that the self-reported measures and the ratings made by nurses, faculty physicians and patients were all significantly intercorrelated.

TABLE 1.—*Pearson Correlation Coefficients Among the Self-reported Humanism Battery and Nurse, Faculty and Patient Ratings*

	Self-report Battery	Nurse Ratings		Faculty Ratings		Patient Ratings
		HUMPTS	HUMSTF	Humanism	Overall Competence	
Self-report Battery	...	.373* (N=64)	.383* (N=64)	.380* (N=50)	.383* (N=50)	.289* (N=74)
HUMPTS		...	.880† (N=85)	.420* (N=50)	.384* (N=50)	.330‡ (N=46)
HUMSTF			...	.390* (N=50)	.356* (N=50)	.320‡ (N=46)
Faculty humanism ratings				...	.816† (N=50)	.397* (N=35)
Overall competence					...	.414* (N=35)
Patient ratings						...

HUMPTS=Humanistic Toward Patients Scale, HUMSTF=Humanistic Toward Staff Scale

*$P<.01$.
†$P<.001$.
‡$P<.05$.

Sociodemographic and Educational Factors

Using the criterion of a .05 level of confidence, no significant relationship was found between any of our measures of humanistic performance and physicians' sex, race, marital status, number of children or a history of divorce or death in the immediate family. Physicians with more siblings, however, had significantly higher scores on the humanism battery ($r=.226, P<.01$).

With regard to educational background, all measures of humanistic performance were unrelated to AOA membership or the number of articles published. Humanistic performance was also unrelated to level of training with one exception: patient satisfaction with art of care was positively correlated with the year of training ($r=.266$, $P<.02$). When this finding was examined further, however, it was found that the statistical significance was due to the small subgroup of faculty physicians who attained very high patient satisfaction ratings. When they were excluded from the analysis, there were no significant differences among levels of training within the house-staff group. Finally, the number of humanities courses taken in college was significantly correlated with the self-reported humanism battery ($r=.173, P<.05$). Also, the number of social science courses taken was significantly correlated with the humanism battery ($r=.195, P<.02$) and with both nurse-rating scales (HUMPTS: $r=.275$, $P<.05$ and HUMSTF: $r=.426, P<.01$).

Premedical Work and Social Experience

In looking at the relationship between physicians' early work and volunteer experiences and their humanism scores and ratings, several interesting findings emerged. As shown in Table 2, physicians who had worked with the disadvantaged or the elderly or who had been involved in a political or social action movement had significantly higher scores on the self-reported humanism battery than physicians who did not have those premedical school experiences. Physicians who had previously worked in a physician's office, a hospital or with children (child care or camp) were rated by supervising faculty physicians on inpatient hospital rotations as being more humanistic than physicians without such experience. Also, overall ratings of clinical competence were significantly correlated with having had previous hospital experience. Patient satisfaction ratings of physicians' humanistic behavior were significantly more favorable among physicians who had worked with children or who had been involved in a social or political action movement. Nurses' ratings of physicians' behavior were generally uncorrelated with physicians' early work experience with one exception: nurses rated physicians who had worked for a political party as significantly less humanistic than those who had not been involved in politics. Finally, when all eight work experiences were combined into an index of work experience, premedical school work experiences were significantly related to higher scores on the humanism battery and higher faculty ratings of both humanistic performance and overall clinical competence (Table 2).

With regard to physicians' reports of the frequency with which they were able to accurately anticipate what their parents were going to say before they said it, Table 2 indicates no relationship between that ability and humanism scores or ratings. Physicians, however, who said they were able to accurately complete a sentence begun by close friends or family more frequently were rated by supervising faculty as being significantly more humanistic and more clinically competent. Finally, physicians who reported that before medical school their friends confided in them about personal problems or turned to them for advice more frequently had significantly higher humanism scores on the self-reported battery and were rated as being more humanistic by the nursing staff.

Discussion

With regard to the hypotheses to be tested in this report, our findings clearly support the confirmation of our first hypothesis: that there are no significant differences in humanism among postgraduate physicians with different demographic characteristics. Marital status, sex, race, number of children, AOA membership, number of articles published or year of training was unrelated to humanism scores or ratings. Therefore, at present there does not appear to be any rationale for using such demographic data to select medical students for postgraduate training to improve the output of humanistic physicians.

The absence of significant differences in humanism scores and ratings among interns and residents also suggests that humanistic attitudes and behaviors (and overall clinical com-

TABLE 2.—*Pearson Correlation Coefficients (and P Values) Between Measures of Humanism and Premedical Work and Social Experience*

Previous Work Experience	Self-report Battery (N=140)	Nurse Ratings		Faculty Ratings		Patient Ratings (N=75)
		HUMPTS (N=65)	HUMSTF (N=65)	Humanism (N=50)	Overall Competence (N=50)	
Physician's office	.098	.095	.045	.312*	.253	.100
Hospital	.076	.196	.080	.332†	.302*	−.058
Child care/camp	−.039	.101	.070	.311*	.083	.254*
Disadvantaged	.197†	.216	.182	.039	−.005	.120
Teaching	.109	.154	.139	−.026	.188	−.030
Elderly/nursing home	.166*	.059	−.031	.181	.182	−.005
Political party	.005	−.250*	−.292†	−.025	.068	−.077
Political/social action	.207‡	−.063	.042	.144	.175	.249*
Work Experience Index§	.216‡	.169	.102	.333†	.322†	.162
Anticipate what parents would say	.022	.119	.039	.082	.134	.084
Accurately complete sentences of others	.024	.154	.039	.328†	.317†	.154
How often friends confided in you	.228‡	.280†	.279†	.003*	−.074	.073
How often people sought your advice	.188*	.315‡	.300†	−.001	−.086	.050

HUMPTS=Humanistic Toward Patients Scale, HUMSTF=Humanistic Toward Staff Scale

*$P<.05$.
†$P<.02$.
‡$P<.01$.
§The sum of the 8 specific work experiences.

petence) might have already matured and developed by the internship year and are not likely to change through postgraduate training. Although a longitudinal study is necessary to confirm this interpretation, these data suggest that in preparing more humanistic physicians, residency programs would be more successful if they recruited and selected more humanistic medical students rather than to expect house staff to develop humanistic attitudes and behaviors or make major changes in them during the postgraduate training experience.

Our second hypothesis stated that physicians with more person-centered or "humanitarian" premedical school work or volunteer experiences would have significantly higher humanism scores and ratings. The data in this report provide some confirmation for this hypothesis although involvement in a political party seems to have a potentially negative effect. Our list of work experiences was by no means exhaustive, but the positive associations of many of such early experiences with self-reported and faculty ratings indicate that gathering historical data on medical students' premedical interpersonal and work-related experiences might be useful in predicting humanistic performance. More work needs to be done in identifying and measuring appropriate historical behavioral data and looking at their predictive validity over time.

The third hypothesis, which stated that the number of social science and humanities courses taken in college would be positively correlated with humanism scores, was also partially confirmed, as was the fourth hypothesis, which stated that a previous history of empathic or help-rendering behavior would be positively associated with ratings of current humanistic performance.

What implications do our findings have for assessing the humanistic performance of postgraduate physicians? The modest but significant intercorrelations between the different evaluation sources including physicians themselves indicate that all have some validity. The modest correlations among sources indicate, however, that no single one should be relied on exclusively or be considered as the gold standard. There seems to be empiric justification for combining information from nurses, patients, supervising faculty and postgraduate physicians themselves to arrive at a more complete and thorough assessment of humanistic performance. Each source has a slightly different perspective on what is humanistic and each can provide insights that can lead to a more comprehensive assessment of a very large and complex set of values, attitudes and behaviors.

What implications do our findings have for using humanistic criteria in selecting medical students for postgraduate training? Again, cross-sectional data, small sample sizes and data from only two highly competitive training programs limit the generalizability of our findings. The significant relationship, however, between all our measures of humanism (including the self-reported battery) and faculty ratings of overall clinical competence suggests that placing more weight on humanistic criteria will not be at the expense of preparing less technically competent physicians. Of course, the findings in this report are based on physicians who have already been accepted into a competitive training program and selected on the basis of traditional academic criteria. Placing more weight on humanistic criteria does not mean that less emphasis should be placed on academic criteria that are currently or routinely used. By adding humanistic criteria, we may be able to increase the output of technically and clinically competent physicians who are also humanistic. Of course, what happens to physicians after residency training cannot be determined from this research.

Finally, the present study has shown that humanistic attitudes and values can be reliably and validly measured by self-report. Together with premedical historical data on course work, premedical work and interpersonal experiences, these or similar materials may be useful to postgraduate training directors or medical schools in selecting students for their educational training programs. Perhaps selection committees in these educational institutions should place more emphasis on applicants' personal data and life experiences, considering them as "hard criteria," and place less emphasis on deans' letters, letters of recommendation and interview data, all of which have been shown to have little predictive validity of clinical or humanistic performance.[22–25] Gathering

personal data and using standardized measures of humanistic attitudes and behaviors require about 30 minutes of respondent time to complete and could be required as part of the application process to either medical school or residency training. There is a need to conduct longitudinal experiments using such data to determine whether or not the number of humanistically oriented, clinically competent physicians can be increased through the addition of humanistic measures to the application and selection process.

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Special Article

Guidelines for the Control of Perinatally Transmitted Human Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and Children

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The transmission of the human immunodeficiency virus (HIV) from infected mothers to infants, either in utero or perinatally, has been well established.[1-10] Infection in these infants can be asymptomatic or cause a variety of clinical syndromes including the acquired immunodeficiency syndrome (AIDS).[11] It is not, however, conclusively known what proportion of infants exposed in utero or perinatally will become infected and in what proportion of infected infants clinical disease will develop.[12] As of December 1, 1985, there were 217 cases of pediatric AIDS reported to the Centers for Disease Control (CDC) (unpublished data). Of these children, 48% were born to intravenous-drug-using mothers, 17% to Haitians and 10% to mothers who either had AIDS or were sexual partners of men with AIDS or at risk for AIDS. An additional 39 (18%) children were infected through transfusions of infected blood or blood products, and 13 (6%) had unknown sources of infection. Thus, 165 (76%) of the cases had been exposed to HIV in utero or perinatally.

HIV Infection in Women of Child-Bearing Age

In the United States, approximately 7% of adult cases of AIDS are women. Nearly 53% of these women are intravenous drug users, 15% are sexual partners of men in risk groups (primarily heterosexual intravenous drug users) and 9% have received infected blood or blood products. In all, 80% are between 20 and 49 years old, 22% of these women are white, 55% black and 23% Latino (CDC, unpublished data). In San Francisco, as of January 31, 1986, there had been ten cases of AIDS reported in adult women. Three of these women were intravenous drug users, one was a sexual partner of a man in a high-prevalence group, four had received transfusions and two had no identified risk. Four were between 20 and 49 years old; two of these were white, one black and one Asian.

HIV Transmission in Households

None of the identified cases of HIV infection in the United States are known to have been transmitted in school, day-care or foster-care settings or through casual person-to-person contact.[13] Other than sexual partners of HIV-infected patients, infants born to infected mothers or a single case involving nosocomial transmission from a child to a mother providing nursing care,[14] none of the family members of the more than 17,000 AIDS patients reported to CDC have had the development of AIDS. Five studies of family members of patients with HIV infection have failed to show HIV transmission to adults who are not sexual contacts of the infected patients or to children who are not already infected perinatally.[15-19] If, however, casual person-to-person transmission of HIV infection does exist, it should theoretically be greatest among young children. This theoretic transmission would most likely involve exposure of open skin lesions of mucous membranes to blood and possibly other body fluids of an infected person. We emphasize that there is no evidence of this type of transmission occurring in any setting at this time.

General Recommendations

Education

Risk-reducing education. All sexually active homosexual, bisexual and heterosexual adults with multiple sexual partners since 1979 should be aware that they are potentially at risk of HIV infection, and sexually active women with multiple sexual partners since 1979 should understand that, if they have been infected, they are at risk of transmitting HIV perinatally. To this end, widespread health education campaigns should address the risk of infection and the ways to prevent sexual transmission among heterosexuals and, more specifically, to women of child-bearing age. Additionally, women in recognized risk groups (Table 1) should be the target of more intensified educational campaigns and, if indicated, special educational programs to decrease their ongoing risk of parenterally or sexually acquiring HIV infection, such as referral for substance abuse or sexual risk-reducing counseling. These campaigns should be culturally and linguistically appropriate for these risk groups.

Provider education. To provide a high standard of care for HIV-infected women, infants and children, obstetricians, pediatricians, foster parents and agencies and other providers

(Rutherford GW, Oliva GE, Grossman M, et al: Guidelines for the control of perinatally transmitted human immunodeficiency virus infection and care of infected mothers, infants and children. West J Med 1987 Jul; 147:104-108)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
CDC = Centers for Disease Control
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus

need to be educated about the virus, its modes of transmission, its prevention and the special issues of confidentiality and counseling surrounding the infection. Focus should be placed on educating and training those providers serving patients at highest risk of infection. We recommend that providers assess each patient's history of potential exposure to HIV and not assume that membership in a risk group implies de facto infection and, conversely, that nonmembership implies noninfection.

Laboratory Testing

We recommend that more than one method of anti-HIV antibody determination be used for testing pregnant women, women in risk groups and children of women in risk groups for HIV infection. Such methods include enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody and Western blot. Because of a possible increased incidence of false-positive ELISA results during pregnancy, especially among intravenous-drug-using women, laboratory testing should be done in a single reliable and experienced facility. Submission of specimens identified only by code number to this laboratory will greatly decrease the chances of unintentional disclosure.

Preconception Recommendations

Whenever possible, women infected with HIV should be confidentially identified and educated about the risks of perinatal transmission. Infected women should be advised to postpone pregnancy until more is known about the specific risks of perinatal transmission. Detailed contraceptive counseling should be offered to these women. Infected women should also be counseled to avoid unsafe sexual practices and to inform previous and prospective sexual partners about their possible exposure. Regardless of other contraceptive methods used, they should use barrier methods of contraception—such as a condom or a condom plus a diaphragm with a nonoxynol-9-containing spermicide—during intercourse to diminish the chances both of transmitting HIV to their sexual partners and of being reinfected with it.

We recommend that women who believe themselves to be at high risk for HIV infection (Table 1) be confidentially or anonymously tested for anti-HIV antibody if they are planning to become pregnant. Testing can be offered through private physicians, alternate test sites or through clinics, especially those used by women in risk groups, such as family planning clinics, drug treatment programs and sexually transmitted disease clinics. Testing of these women, although strongly recommended, must be voluntary and confidential. We do not recommend that women who are not in risk groups be tested at this time. Because of possible sexual contact with men in high-incidence groups, however, it may be prudent for women with multiple sexual partners in areas with a high incidence of AIDS to consider themselves at risk and to obtain preconception counseling and testing if indicated. Regardless of test results, women and their children should continue to have access to all health and social services for which they are eligible.

TABLE 1.—*Women in Whom Human Immunodeficiency Virus Infection Has Been Reported*

Mode of Transmission	*Group*
Sexual	Sexual contacts of AIDS patients or men in risk groups*
	Artificially inseminated women (donor insemination) between January 1, 1979, and June 1, 1985
Parenteral	Intravenous drug users
	Recipients of blood or blood products between January 1, 1979, and June 1, 1985
Either	Mothers of perinatally infected children

AIDS=acquired immunodeficiency virus

*Women with multiple sexual partners in areas with high incidences of AIDS should possibly consider themselves in this category.

Recommendations for Mothers

Identification of Infected Pregnant Women

Routine histories taken at clinical facilities serving women potentially at high risk for HIV infection should include confidential questions designed to elucidate their risk of infection. Such clinics include physicians' offices, family planning clinics, sexually transmitted disease clinics, drug treatment clinics, women, infants and children clinics and prenatal clinics. Written or audiovisual materials, or both, regarding HIV infection should be available at all sites where these women are seen.

We recommend that women in risk groups be educated about HIV infection and that women determined to be at risk be tested at the time they present for prenatal care. Such testing must be voluntary and confidential. We do not recommend routine testing of all pregnant women. High-risk women who are seronegative in the first or second trimester should be retested in the late third trimester to rule out intercurrent HIV infection. Because quality obstetric care requires that the obstetrical provider know if an individual patient is infected, we recommend that, whenever possible, the test be obtained through the provider. Before such testing occurs, however, each provider should institute procedures that guarantee patient confidentiality. A release-of-information form authorizing the newborn's medical provider access to the mother's test result should also be obtained at this time. Because of the unique potential for exposure of health care workers to large amounts of possibly infectious blood and amniotic fluid during the course of labor and delivery, we recommend that labor and delivery personnel be notified of the need for appropriate infection control procedures on a strictly controlled basis. Ideally this information should be transmitted directly to labor and delivery personnel and through a mechanism other than the permanent medical record.

Care of Infected Pregnant Women

These recommendations apply specifically to women who are known to be infected. Guidelines for women at high risk of infection who have not been tested for HIV infection are found under "Special Considerations" below.

Prenatal care. We recommend that any seropositive woman be retested using two different anti-HIV antibody determinations to ensure accuracy. We recommend that women confirmed to be seropositive be carefully counseled regarding the risk of perinatal HIV infection and the options open to

them. Such options include continuing the pregnancy or terminating it if early enough in gestation. Infected women should also be specifically counseled to postpone subsequent pregnancies until more is known about the perinatal transmission of the virus. They should be medically evaluated to rule out any incipient opportunistic infection or malignancy. Specifically, the possibility of infection with *Mycobacterium tuberculosis* should be evaluated by chest x-ray film and purified protein-derivative test, and chronic infection with hepatitis B virus, cytomegalovirus and herpes simplex virus should be excluded. The use of teratogenic drugs, including trimethoprim and most antivirals, should be avoided except in the face of a life-threatening maternal illness.

Intrapartum care. We recommend that hospitals review their procedures for infection control during the intrapartum period and that hospital personnel exercise caution when dealing with any potentially infectious body fluid. For HIV these fluids include blood of either maternal or fetal origin, amniotic fluid and the placenta and membranes. Grossly contaminated linens and disposables, as well as blood and amniotic fluid specimens, should be handled according to the hospital infection control procedures. The choice of location for delivery—delivery room versus labor room—may be dictated by circumstance, but consideration should be given to a labor room delivery to minimize the need for disinfection of two locations. All personnel expected to have direct contact with an infected mother or newborn during delivery should wear gloves and gowns. Those exposed to the possibility of a splash of infectious materials should strongly consider wearing a mask and protective eyewear during the delivery itself. Disposal of all materials should follow hospital infection control procedures. The labor room, delivery room and all instruments should be disinfected with a 1:10 sodium hypochlorite solution. The placenta of a seropositive woman or of a high-risk woman of unknown status should be labeled with "Blood Precautions" or the equivalent before routing for pathologic examination or disposal.

Postpartum care. In the postpartum period, regular hospital infection control procedures for HIV infection should be followed. Isolation of asymptomatic seropositive women is not recommended. Mothers should be given full access to their infants unless they have untreated pulmonary tuberculosis. Until more is known about the possible transmission of virus in breast milk, mothers known to be infected should not breast-feed their infants. Because the potential for exposure to large amounts of infectious material decreases substantially after delivery, information regarding the woman's antibody status should not be transmitted beyond the labor and delivery area, including to social work, law enforcement or correctional personnel.

Special Considerations

Women at high risk of infection who are not tested. We recommend that women at high risk of HIV infection who have not been tested during pregnancy be presumed to be positive for purposes of intrapartum infection control procedures. As the benefits of breast-feeding may outweigh the possible risk of postnatal transmission of the virus, however, breast-feeding by mothers at risk of infection who have not been tested is not absolutely contraindicated. Rather, recommendations regarding the safety of breast-feeding should be individualized and based on a mother's estimated risk of infection.

Intravenous-drug-using mothers. To prevent further parenteral transmission of HIV through needle sharing and further perinatal transmission, we recommend that women in this group be specially targeted for substance abuse treatment and risk-reducing education.

Recommendations for Infants and Children

Identifying Exposed Infants

We recommend that identification of HIV-exposed infants begin in utero. If women in high-incidence groups are not tested during pregnancy, we recommend that for medical reasons their infants be tested as early as possible—such as testing the cord blood—and definitely before 2 months of age. Such testing should be done confidentially and with the voluntary consent of the child's parent or guardian.

Identifying Infected Infants

Infants of seropositive mothers. Infants born to mothers who are known to have been infected during pregnancy should be retested for anti-HIV antibody at about 1 year of age when passively acquired maternal antibody has disappeared. Infants presenting before 1 year of age with symptoms suggestive of HIV infection should be retested at that time. If facilities are available, peripheral mononuclear cells should be cultured for HIV to definitely establish a diagnosis of HIV infection.

Infants and children of high-risk mothers with unknown serologic status. Infants born to mothers at high risk of HIV infection whose prenatal anti-HIV antibody status is not known should be tested before 2 months of age for exposure to HIV and retested at 1 year of age or earlier if clinically indicated. Older children who were born on or after January 1, 1979, and whose mothers were at risk of HIV infection should be tested only if they have not completed a primary series of oral polio vaccine and have not received a measles-mumps-rubella vaccination or if clinically indicated. Because of possible complications of live virus vaccines, we recommend that older high-risk children be tested for HIV exposure or infection before receiving live virus vaccines. In the event that the parent or guardian refuses testing, the infant or child should not receive live virus vaccines.

Infants and children at risk for parenterally acquired infection. Infants and children at risk for parenterally acquired HIV infection should be tested only if they received blood or blood products from a donor identified as HIV-infected and will receive live virus vaccines, or if they were transfused with non-heat-treated factor VIII and will receive live virus vaccines or if clinically indicated.

Infants and children of non-high-risk mothers. Infants and children born to mothers not at high risk of HIV infection and not at risk for parenterally acquired HIV infection should not be tested.

Care of Exposed and Infected Infants and Children

Nursery and in-hospital care. Regular hospital infection control procedures for HIV infection and regular hospital procedures for inpatient care of immunosuppressed patients should be followed in the nursery and during subsequent inpatient admissions. To prevent possible portals of entry for infection, circumcision of exposed male infants should be strongly discouraged and only done with informed consent. Umbilical stumps should be meticulously cleaned daily until they are evulsed.

Routine home care. Care-givers who are exposed to the body fluids and excrement of exposed infants and infected children should be aware of the potential for infection and the modes of HIV transmission. Good handwashing after exposure to body fluids and excrement should be observed and any open lesions, either on care-givers' hands or on children, should be covered.

Medical care. Exposed infants who remain anti-HIV positive beyond 1 year of age or who have documented positive HIV cultures at any age should be considered at risk for the development of AIDS or AIDS-related complex (ARC) and, therefore, potentially immunodeficient. Infants and children either at risk for the development of AIDS or ARC or who have clinical AIDS or ARC should be assumed to have a secondary combined immunodeficiency, be followed closely for problems with growth and development and be given prompt and aggressive therapy for infections and exposure to potentially lethal infections, such as varicella and measles.

Exposed infants and infected children should not receive live virus vaccines or bacille Calmette Guérin until more is known about vaccinating HIV-infected persons. Inactivated vaccines, including *Hemophilus influenzae* type b and pertussis vaccines and diphtheria and tetanus toxoids, are not contraindicated and should be given as regularly scheduled. Inactivated polio vaccine should be substituted for oral polio vaccine and be given in conjunction with diphtheria and tetanus toxoids and pertussis vaccine at 2, 4, 6 and 18 months and 4 to 6 years of age. Measles, mumps and rubella vaccine should not be administered to these children at the present time.

Infants or children with clinical AIDS or ARC should be evaluated and cared for as if they have combined immunodeficiency disease. Because these children potentially have a significant cellular immunodeficiency, all blood products should be irradiated to avoid graft-versus-host disease. Until more is known about the natural history of disease in infants who remain anti-HIV positive beyond 1 year of age, the immune status of these children should be sequentially evaluated with the consultation of a pediatrician experienced in the care of HIV-infected children. The increased risk of *Pneumocystis carinii* pneumonia in these children may be modified by the prophylactic use of trimethoprim-sulfamethoxazole. As these children do not make normal specific antibodies to new antigens, their increased risk of infection with bacterial agents may be altered by monthly administration of immune globulin, either intramuscularly or intravenously.

Special Considerations

Foster care. In each decision involving foster-care placement, a mother's history of possible exposure to HIV infection should be individually assessed to determine if she and her child are truly at risk of infection. In San Francisco these decisions can be made in consultation with a designated perinatal coordinator within the Department of Public Health or, if necessary, with the Perinatal and Pediatric AIDS Advisory Committee. For the purposes of foster-care decisions, the committee in San Francisco also includes consumer advocates representative of ethnic and socioeconomic populations at high risk for perinatally transmitted infection. (For a list of the committee members, see footnote at end of article.)

If a child whose mother has been tested for HIV infection comes to foster care, we recommend that the social worker assigned to the case request that the mother's obstetrical provider release the results of her test to the perinatal coordinator with the mother's consent. Based on the results of these tests, the perinatal coordinator will specify if the infant will need medical foster-care placement or routine foster-care placement. Medical placement will be required for infants of mothers with a positive anti-HIV antibody test and in San Francisco entails review of the placement decision by the Perinatal and Pediatric AIDS Advisory Committee. Routine placement will require that a mother be seronegative. The perinatal coordinator will inform the social worker assigned to follow the child of the reasons for medical placement and will also be responsible, in conjunction with the social worker, for informing the foster family and the child's pediatrician of the reasons for medical placement. Additional authorizations to release information will be required for each of these subsequent disclosures.

Children younger than 3 years currently in foster care and children entering foster care in the future whose mothers were not tested for HIV infection prenatally should be tested for HIV infection only if their mothers have been determined to be at risk of infection. Testing in these cases is indicated on medical grounds alone and should be done with the consent of the mother. In San Francisco, if a mother refuses to consent to testing or refuses to release the results of her test, we recommend that the case be reviewed by the Perinatal and Pediatric AIDS Advisory Committee and, if indicated, confidential testing of the child and release of the test results be done as part of dependency proceedings. Once results of the test are available, they will be released by the child's provider to the perinatal coordinator in the case of voluntary testing or reported directly by the laboratory to the perinatal coordinator in the case of court-ordered testing. The perinatal coordinator will then indicate whether the child is in need of medical placement or routine placement. If the child is in need of medical placement, the perinatal coordinator will follow procedures as outlined above. If, for whatever reason, the child is not tested, the mother's exposure history will be reviewed and appropriate placement recommended by the perinatal and pediatric AIDS advisory committee.

Children in foster care 3 years of age and older, born after January 1, 1979, and born to a mother determined to be at risk of HIV infection should be tested only if they have significant neurodevelopmental delay and lack control of their body secretions or display aggressive behavior, such as biting, or who have uncoverable, oozing lesions. Such testing should occur only after careful medical review by a perinatal and pediatric AIDS advisory committee to determine if such conditions truly increase the theoretic risk of casual HIV transmission. Again, the consent of the child's mother should be obtained for testing and release of information, or, if consent is not available, testing and release of information should be ordered by the court if indicated. We feel that all prenatal testing should be done on a voluntary basis and that the mother should freely consent both to being tested and to release the test results (required by law in California[20]) to assure better medical care of her children. In the event, however, that a mother determined to be at significant risk of infection has not been tested prenatally, refuses to be tested prenatally or refuses to consent to release the results of her prenatal test, as it is our opinion that testing of high-risk children for HIV infection is medically indicated, we recommend that, if these children are to be placed in foster homes, such testing be done and, if necessary, be specifically ordered by the court having

jurisdiction over the child. Before any court-ordered testing, however, the case must be reviewed by the Perinatal and Pediatric AIDS Advisory Committee to determine if testing is indeed indicated.

Adoption. We recommend that infants and children whose mothers were at high risk of HIV infection, who were born on or after January 1, 1979, and who have not been previously tested be tested for HIV infection before placement. We recommend that the HIV status of all children at high risk of infection be made available to adopting parents before final placement so that they can consider the possible social and psychological effects on their families.

Conclusions

The information and recommendations contained in this report were developed and compiled by the Perinatal and Pediatric AIDS Advisory Committee, a special task force of the Department of Public Health, City and County of San Francisco, which included representatives of the Departments of Obstetrics, Gynecology and Reproductive Sciences, Medicine and Pediatrics and the AIDS Activities Unit, San Francisco General Hospital; the Department of Pediatrics, University of California, San Francisco; the San Francisco Medical Society; the American Academy of Pediatrics; the San Francisco Gynecologic Society; the San Francisco AIDS Foundation; Bay Area Addiction Research and Treatment, Inc, and the Department of Social Services, the City Attorney's Office and the Superior Court of the City and County of San Francisco.*

These recommendations apply to all infants, children and women of child-bearing age known to be infected or at high risk of being infected with HIV. This includes persons with CDC-defined acquired immunodeficiency syndrome, persons with lesser clinical manifestations of HIV infection such as ARC and persons with asymptomatic HIV infection. They are intended to supplement previously published national guidelines for the foster care and adoption of HIV-infected children and for the prevention of perinatal HIV infection.

We reemphasize that these are interim guidelines that will need to be reviewed as more information becomes available on perinatal transmission, the natural history of HIV infection in pregnancy and childhood and household transmission and also as vaccine and definitive antiviral therapy become available. Finally, it should be clearly stated that all evidence suggests that there is no risk of casual transmission of HIV and that the primary intent of these guidelines is to assure appropriate medical care for infected pregnant women, infants and children.

*Members of the committee were Moses Grossman, MD, chair: Jeffery W. Amory; Arthur F. Back, DrPH; Paul E. Barnes; Martin C. Carr, MD; Wayne W. Clark, PhD: Daniel E. Collins, JD; Nancy G. Corser, RN, FNP; Dean F. Echenberg, MD, PhD; James R. Green, MD; Marty Jessup, RN, MS; Alan C. Johnson, MD; Ron Kletter, PhD; Craig M. McCabe, JD; Larry Meredith, PhD; Glenn Molyneaux, MD; Geraldine E. Oliva, MD, MPH; Ann O'Reilly, MSW; Nancy H. Rubin, MSW; George W. Rutherford, MD; Edwin S. Sarsfield, MSW; Janet Shalwitz, MD; Nancy S. Shaw, PhD; Florence M. Stroud, MSN, MPH; John R. Vera, MSW; Diane W. Wara, MD; Daniel H. Weinstein, LLB; David Werdegar, MD, MPH; Constance B. Wofsy, MD; Donald F. Wong, MD, and Mark M. Young, MA.

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Editorial Comment

Controlling Perinatally Acquired HIV Infection

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Controlling perinatally acquired infections requires interruption in transmission from mother to infant. Methods used to control other perinatally acquired infections include eradicating infection in mothers and infants through the use of an effective therapy, vaccinating high-risk mothers and infants before infection, doing cesarean section to prevent exposure of an infant and administering hyperimmune globulin to prevent postnatal infection. These methods are either unavailable for or ineffective in controlling perinatally acquired human immunodeficiency virus (HIV) infection. Preventing infection in mothers, pregnancy in infected women and the rare case of postnatal infection through avoiding breastfeeding are the only methods available for the control of perinatal HIV infection. These measures require women and their sexual partners to modify their sexual and drug addiction practices and to suppress often strong desires to bear children. The control problem is further complicated by the fact that women most likely to be infected often come from low socioeconomic populations with poor access to medical care and health education, are usually not highly educated and are often from cultures where discussion of sexual practices between men and women and choosing to remain childless may not be acceptable options. Legal and ethical problems regarding confidentiality and the use of specific HIV diagnostic tests contribute to the difficulty in controlling HIV infection in all groups.

The care of HIV-infected infants involves many controversial medical, social, emotional and legal issues. Specific diagnostic tests to identify infected babies are not adequate and are subject to concerns regarding confidentiality. The decision of whether to give live virus vaccines to asymptomatic HIV-infected children is controversial. Foster care and adoption have been difficult because of the fear of contagion and the lack of special education programs and support for foster families.

The guidelines developed elsewhere in this issue by the San Francisco Perinatal and Pediatric AIDS Advisory Committee address many of these problems. These recommendations, however, cannot be implemented in a "cookbook" style. Planning and discussion of the many complex issues must take place.

Issues Involved in the Control of Perinatal HIV Infection

Preventing infection in women requires the identification of those women who are at increased risk of acquiring HIV infection. Gaining access to these populations can be difficult. The availability and use of health care facilities are often limited in populations characterized by intravenous drug abuse, low socioeconomic status and minority race or ethnicity. This problem should be addressed by the appropriate assessment of community health care resources and provision of resources when necessary.

To identify infected women and those at increased risk of infection, appropriate screening programs must be developed. The type of clinics where these programs should be placed and the information to be elicited are described in the San Francisco guidelines. Personal information regarding sexual practices and drug abuse must be obtained confidentially and in a manner that is sensitive to the cultural and language needs of a patient. Although the guidelines stress counseling for women at increased risk of infection, some education regarding HIV infection and its transmission should be provided to all sexually active women. This will become particularly important as the prevalence of infection rises in the heterosexual population.

Once high-risk women have been identified, their infection status should be determined so that counseling and referral for care can be tailored to their needs as outlined by Rutherford and colleagues in the San Francisco guidelines. Alienation and discrimination towards infected patients have limited the use of HIV diagnostic tests, however. Community legal systems must assure that the rights of infected persons are preserved. Much of the alienation is due to unwarranted fears of contagion. It is the responsibility of the public health system in cooperation with community leaders to dispel these fears through continual education of the public and news media and to press forward with counseling and testing.

Women at increased risk must be counseled to modify their behavior. Women who abuse drugs intravenously need to enter and remain in treatment programs and stop such behavior. In many communities, however, the availability of such programs is limited. These resources need to be assessed and adequate facilities provided. The quality of the programs must also be assessed. Rehabilitation should be comprehensive, including altering drug-use behavior, improving overall health status and providing social and employment needs.

Treatment may not be effective in some addicted women. Some persons undergoing methadone maintenance treatment continue to abuse cocaine and even heroin intravenously. Education and counseling regarding needle-sharing practices may not be effective in eliminating this practice in those who continue to abuse drugs. Drug abusers may not be able to obtain or afford new needles and possession of drug-abusing paraphernalia is illegal in some places, a law which may promote the use of "shooting galleries." Drug abusers should be instructed on needle-decontamination techniques. Alternative approaches such as "needle exchange" programs that allow drug abusers to exchange contaminated needles for clean ones need to be considered and evaluated.

Women at risk of acquiring or transmitting HIV infection

(Rogers MF: Controlling perinatally acquired HIV infection. West J Med 1987 Jul; 147:109-110)

Reprint requests to Martha F. Rogers, MD, Chief, Pediatric and Family Studies Section, AIDS Program, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA 30333.

ABBREVIATIONS USED IN TEXT

ACIP = Immunization Practices Advisory Committee
AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

through sexual exposure must insist that their infected partners wear condoms and limit their sexual contact to practices that do not involve the exchange of body fluids. Some women may be from cultures where discussion of sexual practices between men and women is not accepted. Counseling designed to alter sexual practices must include both partners and must be sensitive to cultural demands.

The San Francisco guidelines stress the need for infected women to be counseled to postpone pregnancy "until more is known." Preliminary data from prospective studies of pregnant women and their infants suggest that the frequency of transmission from mothers to infants may be as high as 50% and that symptoms of infection may develop in most infected infants. If these data are confirmed and if no vaccine or effective therapy becomes available, then preventing perinatal infection would require that these women not bear children at any time because most will be infected for many years or perhaps for life. Effective contraception requires that clinics be available, used and staffed with personnel sensitive to the needs of these women. The use and effectiveness of birth control measures in these populations of women should be studied.

Issues Involving the Care of Infected Infants

Identifying infected infants involves many of the same problems encountered in identifying infected women, including poor access to medical care and confidentiality issues. In addition, diagnosing HIV infection in infants is difficult because there are no standardized, widely available tests for detecting virus infection. Tests for antibody to HIV identify only exposed infants because maternal antibody will be present in all infants born to seropositive women. Virus culture is expensive, not widely available and is not very sensitive. Serologic tests for viral antigen have been developed, but their usefulness in diagnosing infection in infants is currently unknown. Until more definitive diagnostic methods are available, all infants born to seropositive women should be closely followed and evaluated as described in the San Francisco guidelines.

The issue of whether asymptomatic seropositive children can be vaccinated with live virus vaccines is controversial. Based on the lack of reported adverse reactions to these vaccines, the Immunization Practices Advisory Committee (ACIP) has recommended that "such persons should be vaccinated with [measles, mumps, rubella] in accordance with [other] ACIP recommendations." However, the Canadian National Advisory Committee on Immunization has recommended that "it is prudent to defer administering live vaccines to known asymptomatic [human T-lymphotropic virus type III/lymphadenopathy-associated]-infected persons until further data make a more informed and definitive recommendation possible." The San Francisco guidelines agree with the Canadian recommendation. The danger of this recommendation is that these children will be susceptible to the wild disease, which may be more severe in HIV-infected children, particularly later in life when their immune systems may have deteriorated. In addition, as HIV infection becomes more prevalent, more children will remain susceptible (unvaccinated), increasing the likelihood of epidemics. Clearly, this issue needs further study.

Many HIV-infected children require foster care because their mothers are drug-addicted and unable to care for them or because their mothers may have died of the acquired immunodeficiency syndrome (AIDS). Agencies responsible for the foster care of HIV-infected children should establish programs for educating foster families regarding the importance of aggressive medical care for these children and the need to observe precautions to prevent possible household transmission. The San Francisco guidelines recommend special medical placement for seropositive children.

The guidelines also recommend that children born to high-risk mothers be tested for HIV infection before their placement in foster or adoptive homes. Although the reasons stated are valid, identification of infected children will undoubtedly increase placement difficulties. Finding foster care and adoptive families for HIV-infected children is difficult because of the fear of contagion and the unwillingness of some foster or adoptive families to accept children who may require a lot of medical care and who may be terminally ill. The most successful foster-care programs have been those that provide special financial and other support for these families.

The prevention of perinatal AIDS and the care of HIV-infected children require consideration of many complex issues. While the problem of pediatric AIDS in San Francisco may be small in terms of the number of infected children, it is unlikely to remain so. If infection rates in the drug-abusing population increase, perinatal infection will also increase. Bisexual men who engage in high-risk sexual contact with members of the gay community will become infected and transmit the virus to their female sexual partners. The importance of these recommendations for preventing perinatal HIV infection and the care of infected children should not be underestimated. It is the responsibility of both the health department and health care and other organizations serving these populations of women to assure that prevention programs are developed, implemented and evaluated according to the recommendations. Other communities need to develop similar recommendations based on the circumstances in their community.

Clearly the tools available to us for preventing HIV infection are minimal. The need to develop other, more effective, methods of intervention is great. Development of an effective vaccine and irradiative therapy for HIV should receive the highest priority. Studies to determine the timing of mother-to-infant transmission and whether or not cesarean section or the use of hyperimmune globulin would be effective in preventing transmission to infants are needed, as are appropriate planning and organizing at the federal, state and local levels to assure the effective and efficient use of available resources in the fight against the spread of the AIDS epidemic.

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(Continued from Page 31)

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NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 20-23—**Annual Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Mon-Thurs. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

August 7-8—**16th Annual Santa Fe Cardiology Symposium—Controversies in Cardiovascular Disease Management.** Hotel Eldorado, Santa Fe. Fri-Sat. Contact: Santa Fe Cardiology Symposium, 1101 Medical Arts Ave NE, Albuquerque 87102. (505) 842-8321.

September 11-13—**Essentials of Health Care for the Elderly.** UNM Conference Center, Albuquerque. Fri-Sun. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

September 19—**Practical Management of Diabetic Foot Infections.** Veterans Administration Medical Center, Albuquerque. Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

September 24-26—**Concepts and Controversies in Perinatal Care.** Holiday Inn Journal Center, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME. (505) 277-3942.

September 24-26—**Wilson Lectureship—Cardiology Symposium.** Albuquerque. Thurs-Sat. Contact: Presbyterian Heart Institute Cardiology Symposium, PO Box 26666, Albuquerque 87125. (505) 841-1065.

October 1-3—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

October 10-11—**Pediatric Chronic Diseases.** Santa Fe. Sat-Sun. Contact: Marilyn Stack, Executive Secretary, New Mexico Pediatric Society, (505) 265-7431.

October 23—**Update in Cardiology.** Albuquerque. Fri. Contact: Charles Karaian, MD, 1101 Medical Arts Ave NE, Albuquerque 87102. (505) 842-8321.

October 23-25—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Fri-Sun. Contact: The Presbyterian Heart Institute, Barry W. Ramo, MD, (505) 242-2796.

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(Continued on Page 114)

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INTERNAL MEDICINE. San Francisco suburb. BC/BE associate needed for busy solo practice adjacent to Mount Diablo Hospital. Send CV to Number 41, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 111)

November 13-14—**New Mexico Medical Society Interim Meeting—Risk Management.** Sally Port Inn, Roswell. Fri-Sat. Contact: NMMS, (505) 266-7868.

December 3-5—**American College of Physicians, New Mexico Chapter—Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

December 11-12—**Trauma Update '87.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: Latter-Day Saints Hospital, 325 8th Ave, Salt Lake City 84143. (801) 350-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

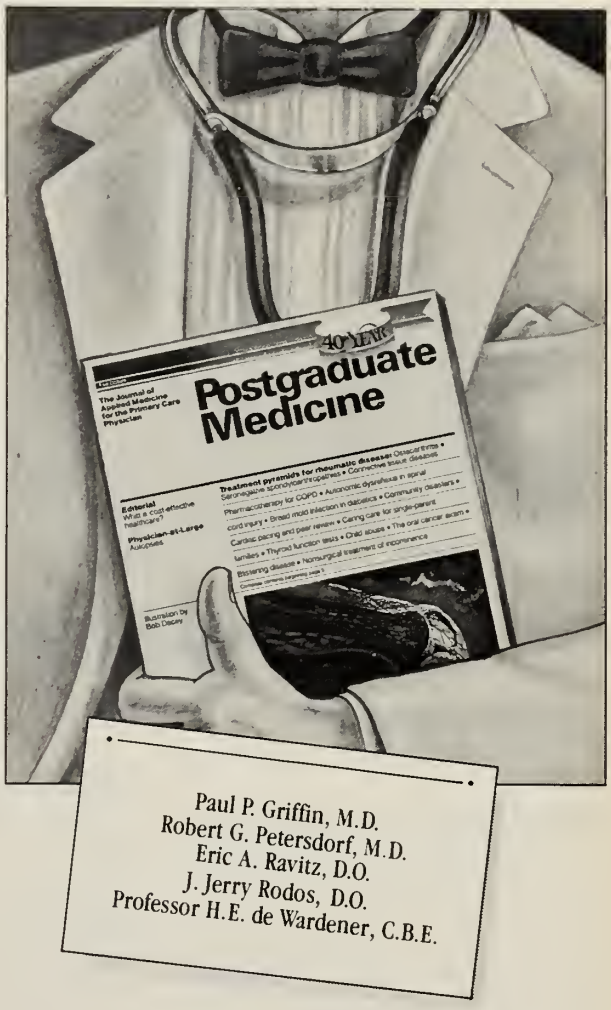
UVH: Utah Valley Hospital, 1034 N Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 118)

FAMOUS PHYSICIANS ARE SHOWING UP FOR OUR 40th YEAR CELEBRATION.



Paul P. Griffin, M.D.
Robert G. Petersdorf, M.D.
Eric A. Ravitz, D.O.
J. Jerry Rodos, D.O.
Professor H.E. de Wardener, C.B.E.

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July
Symposium: Skeletal Problems
Special Article: Orthopedics 1947-1987 . . . . . Paul P. Griffin, M.D.

August
Symposium: Infectious Diseases
Special Article: Infectious Diseases 1947-1987 . . . . . Robert G. Petersdorf, M.D.

September 1
Symposium: Focus on Osteopathic Medicine . . . . . Eric A. Ravitz, D.O. Coordinator
Special Article: Osteopathic Medicine 1947-1987 . . . . . J. Jerry Rodos, D.O.

September 15
Symposium: Renal Disease
Special Article: Renal Disease 1947-1987 . . . . Professor H.E. de Wardener, C.B.E.

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Postgraduate Medicine

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FHP is a well-established and progressive HMO and we enjoy proximity to and support of several university programs in the area. Our steady growth coupled with the opening of our own 125-bed hospital last year, has created career opportunities for BC/BE Primary Care Physicians. For more information about joining our progressive team of professionals, please write or call (800) 446-2255, or (800) 336-2255 within California.

FHP

Professional Staffing, Dept. 45
9900 Talbert Avenue
Fountain Valley, CA 92708

(Continued from Page 114)

PHYSICIANS WANTED

ORTHOPAEDICS. Excellent private practice opportunities currently available in New Mexico and Colorado communities. Income guarantee/financial assistance available; relocation allowance provided. Wide range of recreational opportunities. For further information, please contact Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

PHOENIX, ARIZONA. Well-established head and neck surgeon interested in sharing his practice. Reply to Number 44, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SEVERAL FAMILY PRACTICE opportunities in the growing south Snohomish/north King County area of Washington state. Edmonds is in the greater Seattle area and noted for its quality of life. One physician needs an associate; another is retiring and needs someone to take over. Contact Greg Falk, Stevens Memorial Hospital, 21600 76th Ave W., Edmonds, WA 98020; (206) 774-0555.

BC/BE INTERNIST to join progressive HMO in the San Francisco bay area. Position is at a satellite clinic in Sonoma County. Excellent benefits. Outstanding educational, cultural and recreational opportunities. Contact Jonathan Freudman, MD, Assistant Chief of Medicine, Kaiser Permanente, 99 Montecillo Rd, San Rafael, CA 94903. AA/EEO Employer.

INTERNIST/PHOENIX, ARIZONA. Busy General Internist, solo here for six years, is now seeking an associate. There is also an opportunity to associate with a young DO. For further information, call or send your CV to Gordon Crawford, Humana Inc, Dept. G-7, 500 W. Main St, Louisville, KY 40201-1438. Toll-free (800) 626-1590.

PHYSICIANS WANTED

PHYSICIAN RECRUITMENT. Position available in San Francisco Area Medical Network, seeking physician with an interest in a stable, long-term practice opportunity in ambulatory care. Enjoy the advantages of private practice without the cost and complications. Candidate must be BC/BE in either Family Practice or Internal Medicine. Interested-send CV to Dr Susann Steinberg, 5748 Geary Blvd, San Francisco, CA 94121; (415) 668-4005.

OLYMPIA, WASHINGTON. Primary Care preferred for vacancy in medical complex—independent practice—with loose association for call coverage. Will introduce qualified practitioner. Presently three FPs and one Internist in the complex, none of them are young. Contact Edmund Olson, MD, 1015 W. 4th, Olympia, WA 98502; (206) 357-4201.

INTERNIST. Four BC/BE physicians in Internal Medicine for private practice style office scheduled to open September 1 in Redding, California under the auspices of the Veterans Administration. Send CV and references by August 1 to Jon Green, MD, PhD, 150 Muir Rd, Martinez, CA 94553. Equal Opportunity Employer.

FAMILY PRACTICE/INTERNAL MEDICINE/ENDOCRINOLOGY/CARDIOLOGY/OCCUPATIONAL MEDICINE physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing southwest community (population 500,000 plus). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics/Internal Medicine/Subspecialties/24-hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with CV to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645.

PHYSICIANS WANTED

OPPORTUNITY FOR GENERAL INTERNIST. Expanding academic group practice seeks additional General Internist in the Division of General Internal Medicine. Combined fee-for-service/prepaid patient mix. Duties include 80% clinical practice in multispecialty faculty private practice group, 20% teaching residents and students ambulatory care and inpatient medicine. Competitive salary and benefits. Equal Opportunity Employer. Send CV to Sophocles Panagon, MD, General Internal Medicine, University of California, Irvine Medical Center, 101 City Dr South, Route 81, Orange, CA 92668.

ARIZONA EMERGENCY MEDICINE. An emergency department Medical Directorship and staff positions are immediately available at two client hospitals located in Kingman and Lake Havasu City. Moderate volume emergency departments. Excellent nursing and medical staff support. We offer a guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. Directors also receive paid health benefits which include dependents. For additional information contact George Tracy, Spectrum Emergency Care, 6275 Lehman Dr, Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

FAMILY PRACTICE PHYSICIANS. Immediate opportunities available. Establish own practice with lease agreement at established medical center, located approximately 90 miles from Phoenix in Salome, Arizona. Holbrook, Arizona needs Family Practice physician with OB (back up available); first year malpractice paid; guaranteed salary plus additional benefits. Located 90 miles from Flagstaff. Contact: AHPR, 3131 E. Second St, Tucson, AZ 85716; (602) 626-7946.

(Continued on Page 117)

(Continued from Page 116)

PHYSICIANS WANTED

HOUSE PHYSICIANS

These day and evening openings allow you to practice in our comfortably-sized, 200-bed acute care hospital in a beautiful San Francisco neighborhood. Positions start July 1 and cover ICU patients. Direct inquiries to Dr Rosenstein, (415) 386-7000.

MARSHAL HALE MEMORIAL HOSPITAL

FAMILY PRACTICE IN IDAHO? Join four physicians and nine nurse practitioners in an exciting clinic system. One position available in September 1987. Attractive salary and benefit package. Contact Erwin B. Teuber, PhD, Administrator, or Robert LeBow, MD, Medical Director, Terry Reilly Health Services, 211 16th Ave North, Nampa, ID 83651; (208) 467-4431.

IDAHO NEEDS FULL-TIME EMERGENCY PHYSICIAN. 20 miles from Boise, near mountains and unlimited recreation. Excellent opportunity to affiliate with 162-bed hospital. ACLS-yes. Contact M. Kutsurelis, Vice President Administrative Services, Mercy Medical Center, 1512 12th Ave Road, Nampa, ID 83651; (208) 467-1171.

FEMALE FAMILY PRACTITIONER wants help caring for young, healthy families. Some obstetrics, flexible schedule; possible temporary or permanent partnership. PO Box 819, Mendocino, CA 95460; (707) 937-4272.

LAKEWOOD HOSPITAL, SOUTH PUGET SOUND, recruiting for associates in: Family Practice and Internal Medicine; is a 95-bed acute care surgical, medical, and obstetrical hospital which has a new facility due for early 1988 completion. In addition, a very busy associate physician wishes to retire from his solo practice in Internal Medicine. This practice, which was established and has run consistently since 1966, is for sale. Lakewood is the "Lake District" of south Puget Sound surrounded by the Olympic Mountains, the Cascades and Mt. Rainier which provide outstanding water and mountain recreational activities. BC/BE respond to Genie Latta, Physician Recruitment, Lakewood Hospital, 5702 100th St S.W., Tacoma, WA 98499-0998; (206) 588-1711.

THE COMMUNITY OF ARTESIA, NEW MEXICO is seeking a Board certified or eligible General Surgeon to establish a private practice. Fully-equipped office with established referral patterns available for purchase. Community-based financial assistance may be available to the right individual. Artesia is a community of 14,000 located in southeast New Mexico. A great place to raise a family—peaceful community with year 'round recreation and excellent weather. Fully-equipped, 38-bed new hospital. Please submit CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

GENERAL SURGEON BC/BE. Excellent opportunity to associate in a busy surgical practice in Sonoma, California, one hour drive north of San Francisco. Contact J. Basil Haddad, MD, 181 Andrieux St, Sonoma, CA 95476; (707) 996-6119.

EXCELLENT TEXAS OPPORTUNITIES. ENT, Family Practitioner, General Practitioner, General Surgeon, Internal Medicine, OB/GYN person, Ophthalmologist, Oncologist, Pediatrician, Radiation Oncologist to practice in one of several lake area communities, in the beautiful Piney Woods area of east Texas. Enjoy boating, fishing, hunting year 'round. Excellent quality of life, first year guarantee, etc. Other Texas opportunities available also. Reply with CV to Medical Support Services, Armando L. Frezza, 11509 Quarter Horse Trail, Austin, TX 78750; (512) 331-4164.

(Continued on Page 120)

THE ARMY NEEDS PHYSICIANS PART-TIME.

If you are a practicing physician who wants a break from your daily practice . . . while still practicing high-quality medicine and serving your country . . . consider an officer commission in the ARMY RESERVE MEDICAL CORPS.

AMONG THE BENEFITS:

- Subsidized professional development which could include two conferences/short courses of your choice.
- Up to $50,000 Group Life Insurance package, nominally priced for qualifying MD's, generous retirement annuity to qualifying physicians at age 60.
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- Post Exchange, Commissary (during Annual Training) and space-available travel on military aircraft.
- Flexible training programs that won't interfere with your practice.

To see if you qualify contact:

Major Patricia S. Schackleton, MSC	415-751-1616
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Captain Gregory F. Linden, MSC	619-453-9937

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CONTINUING MEDICAL EDUCATION

(Continued from Page 115)

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

August 7-8—**Utah Ophthalmological Society Shakespearean Festival Meeting** (Sponsor: UOS). Fri-Sat. Southern Utah State College, Cedar City, Utah. 7 hrs. Contact: Maxcine Frye, (801) 355-7477.

August 24-28—**Occupational Epidemiology** (Sponsor: UUMC). Mon-Fri. College of Nursing, Univ of Utah, Salt Lake City. 32.5 hrs. Contact: Connie Crandall, (801) 581-5710.

August 31-September 4—**Environmental Epidemiology and Risk Assessment** (Sponsor: UUMC). Mon-Fri. College of Nursing, Univ of Utah, Salt Lake City. 32.5 hrs. Contact: Connie Crandall, (801) 581-5710.

September 9-11—**Utah State Medical Association Annual Meeting.** Marriott Hotel, Salt Lake City. Wed-Fri. Contact: USMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-5290.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 19-23—**Reducing Risks From Environmental Chemicals Through Biotechnology.** Seattle. Sun-Thurs. NW Center for Occupational Health and Safety. Contact: U/W.

July 24-26—**WSSA: Seafair IX Regional Anesthesia.** Seattle. Fri-Sun. Virginia Mason Medical Center. Contact: VMMC.

October 1-2—**American College of Emergency Physicians—17th Annual Fall Scientific Assembly.** Seattle. Thurs-Fri. Bellevue Red Lion Inn. Contact: Washington Chap. ACEP, (206) 441-9762.

November 27-December 10—**Emergency and Critical Care Downunder.** Sites in New Zealand and Australia. Fri-Thurs. Contact: Washington Chapter, American College of Emergency Physicians, Georgine Elich, Kailani World Travel, 1 (800) 542-5264 or (206) 671-1800. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

News from DISTA about a new dosage form of cephalexin

ANNOUNCING NEW

Keflet™ TABLETS

cephalexin

All the advantages of cephalexin in a convenient tablet form

- Backed by over 15 years of clinical experience
- Smaller tablet is specially shaped and coated for easier swallowing
- May enhance patient compliance, particularly among the elderly
- Tablet dosage form may be appreciated by patients of all ages

NEW Keflet Tablets are available as:

250-mg Tablets

500-mg Tablets

Keflet is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-sensitive patients.

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Brief Summary Consult the package literature for prescribing information.
Indications and Usage: Keflet™ Tablets (cephalexin, Dista) are indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

Respiratory tract infections caused by *Streptococcus pneumoniae* and group A β hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflet is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflet in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media due to *S pneumoniae, Haemophilus influenzae,* staphylococci, streptococci, and *Neisseria catarrhalis*

Skin and skin-structure infections caused by staphylococci and/or streptococci

Bone infections caused by staphylococci and/or *Proteus mirabilis*

Genitourinary tract infections, including acute prostatitis, caused by *Escherichia coli, P mirabilis,* and *Klebsiella* sp

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Contraindication: Keflet is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keflet.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes of colitis should be ruled out.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: *General*—Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflet occurs, the drug should be discontinued and the patient treated with the usual agents (eg, epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keflet may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Keflet should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflet, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—The daily oral administration of cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, fetal viability, fetal weight, or litter size. Note that the safety of cephalexin during pregnancy in humans has not been established.

Cephalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. Nevertheless, because the studies in humans cannot rule out the possibility of harm, Keflet should be used during pregnancy only if clearly needed.

Nursing Mothers—The excretion of cephalexin in the milk increased up to 4 hours after a 500-mg dose; the drug reached a maximum level of 4 μg/mL, then decreased gradually, and had disappeared 8 hours after administration. Caution should be exercised when Keflet is administered to a nursing woman.

Adverse Reactions: *Gastrointestinal*—Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity—Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson Syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, neutropenia, thrombocytopenia, and slight elevations in SGOT and SGPT have been reported.

PV 2211 DPP

[111786]

Additional information available to the profession on request from

DISTA

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285
Mfd by Eli Lilly Industries, Inc
Carolina, Puerto Rico 00630

720073

(Continued from Page 117)

PHYSICIANS WANTED

FAMILY PRACTICE PHYSICIAN—SANTA FE, NEW MEXICO. BC/BE, six months OB training. Share call with two MDs. Much obstetrics. Send CV to Arturo Gonzales, La Familia Medical Center, PO Box 5395, Santa Fe, New Mexico 87501; (505) 982-4427.

SEEKING A PHYSICIAN TO ASSOCIATE with a Family Practice group. Ultramodern facility with outpatient surgical suite. Located in Corona, California, between Orange County and San Diego. Growing area; good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes, (714) 734-3042.

INTERNIST. Live in San Francisco and commute to nearby rural area for four two-night shifts per month in combined Internal Medicine–Emergency room practice. Four Internists currently working in stable group. Practice quality medicine in the country where you can make a greater impact and enjoy lots of free time wherever you like to live. $60K per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

CALIFORNIA, NEAR MOUNTAINS AND SEA COAST. Immediate openings for BC/BE Physicians. Combination urgent-care, Workmens' Compensation and family medicine. Full-time opportunities with expanding practices. Growth oriented physician group, Reply with CV to PO Box 14057, Pinedale, CA 93650.

BC/BE INTERNIST OR FAMILY PHYSICIAN needed for busy multispecialty group in Durgano, Colorado. Practice next to hospital, beautiful surroundings; benefits provided. Contact Bonnie DuPuis, PO Box 2637, Durango, CO 81302, or call (303) 247-2611.

EDMONDS, WASHINGTON. Scenic waterfront community 20 minutes north of Seattle. Physician owned clinic combined OB/GYN and Family Practice seeks additional OB/GYN for full- or part-time. We presently have 4 Family Practitioners and 2 OB/GYNs. Send CV to Philip DuBois, MD, 7935 216 St SW, Ste E, Edmonds, WA 98020; (206) 775-0681.

Medical Director IPA

West Coast Division of CIGNA Healthplan, Inc. is seeking a physician with considerable administrative and clinical experience for a management position in established and fast-growing company headquartered in Glendale, CA. The individual must have specialty boards, excellent interpersonal skills, and must have IPA experience including utilization management, quality assurance and physician contracting. Send curriculum vitae with desired salary in confidence to: Fran Weekly, Director/Professional Recruitment, 505 N. Brand Blvd., Suite 400-49, Glendale, CA 91203.

investigate idaho

PSYCHIATRIST

Immediate position available in one of Idaho's largest and most progressive medical centers. This medical center possesses the latest in technology; its medical staff has 293 members, representing all specialities. Affiliated with the University of Washington, the medical center sponsors a busy, successful family practice residency program.

The Psychiatrist position will participate in setting the direction for psychiatric services.

The position responsibilities include directing and supervising a multi-disciplinary treatment team, coordinating a quality assurance program, specified administrative responsibilities, education, in-house consultation and community involvement.

The generous salary and benefit programs include vacation and educational leave, malpractice insurance, a complete benefit package and an attractive bonus plan.

The medical center is located in Boise, Idaho, a community surrounded by the best outdoor opportunities in the country, including skiing, white water rafting, hunting and fishing.

Please send inquiries and resumes to:

Connie Perry
Vice President-Speciality Services
St. Alphonsus Regional Medical Center
1055 N. Curtis Road, Boise, ID 83706

member, Holy Cross Health System
An Equal Opportunity Employer M/F

PHYSICIANS WANTED

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Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1988, date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1988, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1988, date and place to be announced.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-5290. Annual Meeting: September 9-11, 1987, Marriott Hotel, Salt Lake City.

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ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

MICROBIOLOGY. The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage):

GRAM-NEGATIVE AEROBES: *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*.

Note: Many strains of the above organisms that are multiply resistant to other antibiotics, *e.g.* penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium.

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*.

GRAM POSITIVE AEROBES: *Staphylococcus aureus* (including penicillinase-producing strains) and *Staphylococcus epidermidis* (Note: methicillin resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note: Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant.)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown.

GRAM NEGATIVE AEROBES: *Citrobacter freundii, Citrobacter diversus, Providencia* species (including *Providencia rettgeri*), *Salmonella* species (including *S. typhi*), *Shigella* species and *Acinetobacter calcoaceticus*.

ANAEROBES: *Bacteroides* species, *Clostridium* species (Note: most strains of C. *difficile* are resistant).

SUSCEPTIBILITY TESTING. Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45: 493-496, 1966, Standardized Disk Susceptibility Test, *Federal Register* 39: 19182-19184, 1974, National Committee for Clinical Laboratory Standards, Approved Standard: ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975.) has been recommended for use with disks to test susceptibility to ceftriaxone.

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria:

1. Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.
3. Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks.

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone.

Standardized procedures require use of control organisms. The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853, respectively.

DILUTION TECHNIQUES. Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml. Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml. Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

E. coli ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests. Greater than 95% of MICs for the *E. coli* strain should fall within the range of 0.016 to 0.5 mcg/ml. The range for the *S. aureus* strain should be 1 to 2 mcg/ml, while for the *P. aeruginosa* strain the range should be 8 to 64 mcg/ml.

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*.

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*.

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae, Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*.

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*.

PROPHYLAXIS. The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery.

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

SUSCEPTIBILITY TESTING. Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

ROCEPHIN® (ceftriaxone sodium/Roche)

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*.

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic associated pseudomembranous colitis produced by C. *difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: *GENERAL*. Although transient elevations of BUN and serum creatinine have been observed at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY. Carcinogenesis. Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis. Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility. Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY. Teratogenic Effects. Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects. In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS. Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE. Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after IV administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia.

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM: headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours. Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

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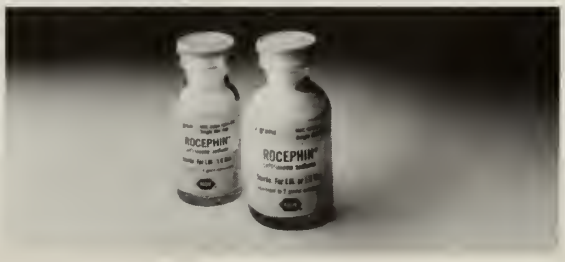

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The portrait of anxiety

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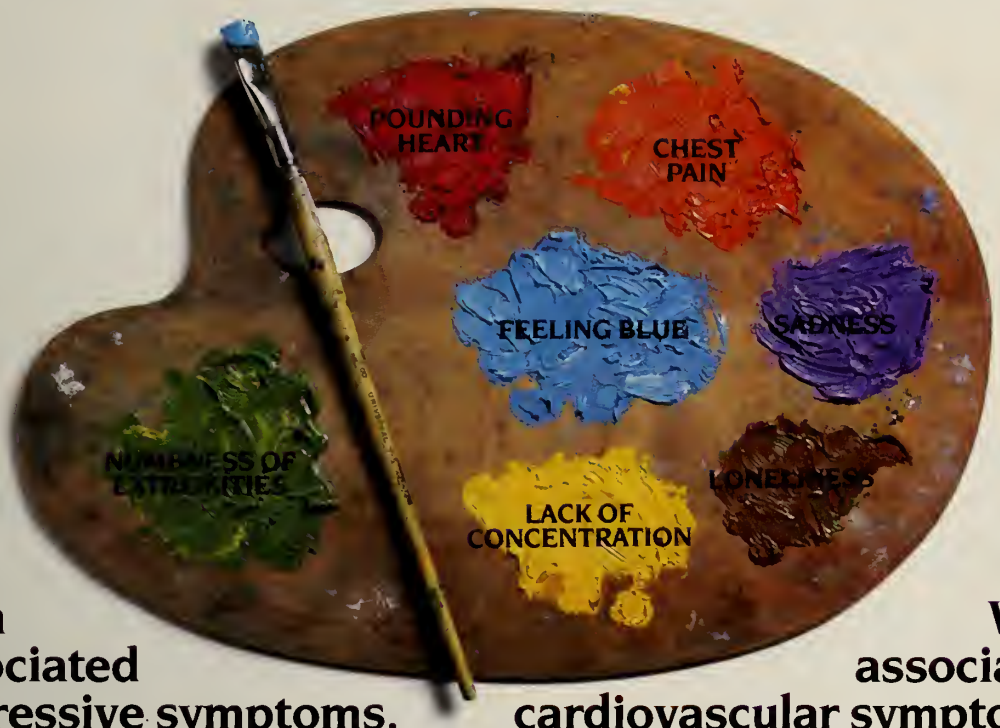
is often complicated



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Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

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168 **Pathogenesis of Sarcoidosis**
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From the Department of Medicine, Pulmonary Disease Section, Sarcoidosis Clinic, Los Angeles County-University of Southern California Medical Center, Los Angeles.

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175 **The Neurologic Sequelae of Cardiac Arrest**
Discussant: W. T. LONGSTRETH, Jr, MD, MPH
A discussion selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it was edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

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181 **New Approaches to Treating Systemic Lupus Erythematosus**
Discussant: DAVID WOFSY, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Urology
Items of progress in urology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

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STUART D. BOYD, MD

188 **Ureterorenoscopy**
JEFFRY L. HUFFMAN, MD

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In mild-to-moderate hypertension†

CAPOTEN (captopril tablets)

THERE'S SAFETY IN OUR NUMBERS

• 8 years in clinical use
CAPOTEN has an established record of practical clinical usage, spanning nearly a decade.

• 16 million prescriptions
Since its successful introduction in the U.S., CAPOTEN has earned the prescribing confidence of physicians.[1]

• 5 million patients
CAPOTEN has provided well-tolerated therapy for over 5 million patients worldwide.

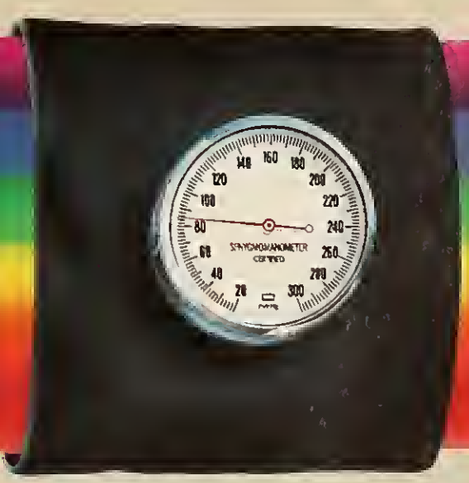
• 3,000 clinical papers
More than 3,000 informative articles have been published about CAPOTEN.

Convenient, well-tolerated therapy that promotes patient compliance

Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)‡[1]

ADVERSE EFFECT	CAPOTEN (N=1,174) (% affected)	Placebo (N=448) (% affected)
Headache	5.2	6.9
Rash	3.7	2.5
Dizziness	3.5	2.0
Nausea	3.2	2.0
Fatigue	3.1	2.0
Taste alteration	1.5	1.1
Gastrointestinal	1.4	0.7
Diarrhea	1.1	1.1

‡None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.



†CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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CAPOTEN® captopril tablets LOW DOSE

FIRST-LINE THERAPY THAT PUTS QUALITY OF LIFE FIRST

*Angiotensin Converting Enzyme

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CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (~150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

References:

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2. Data on file, Squibb Institute for Medical Research.

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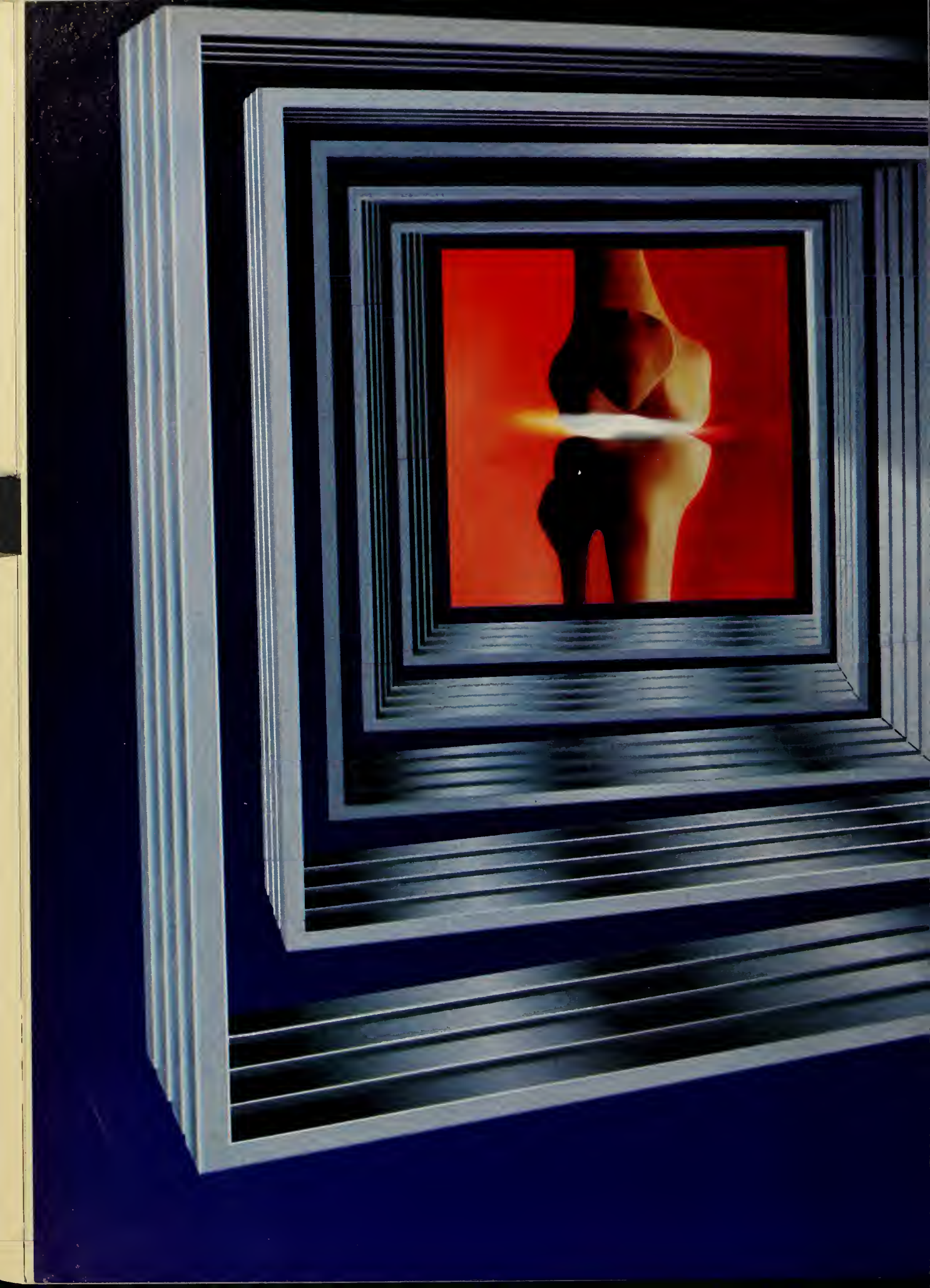

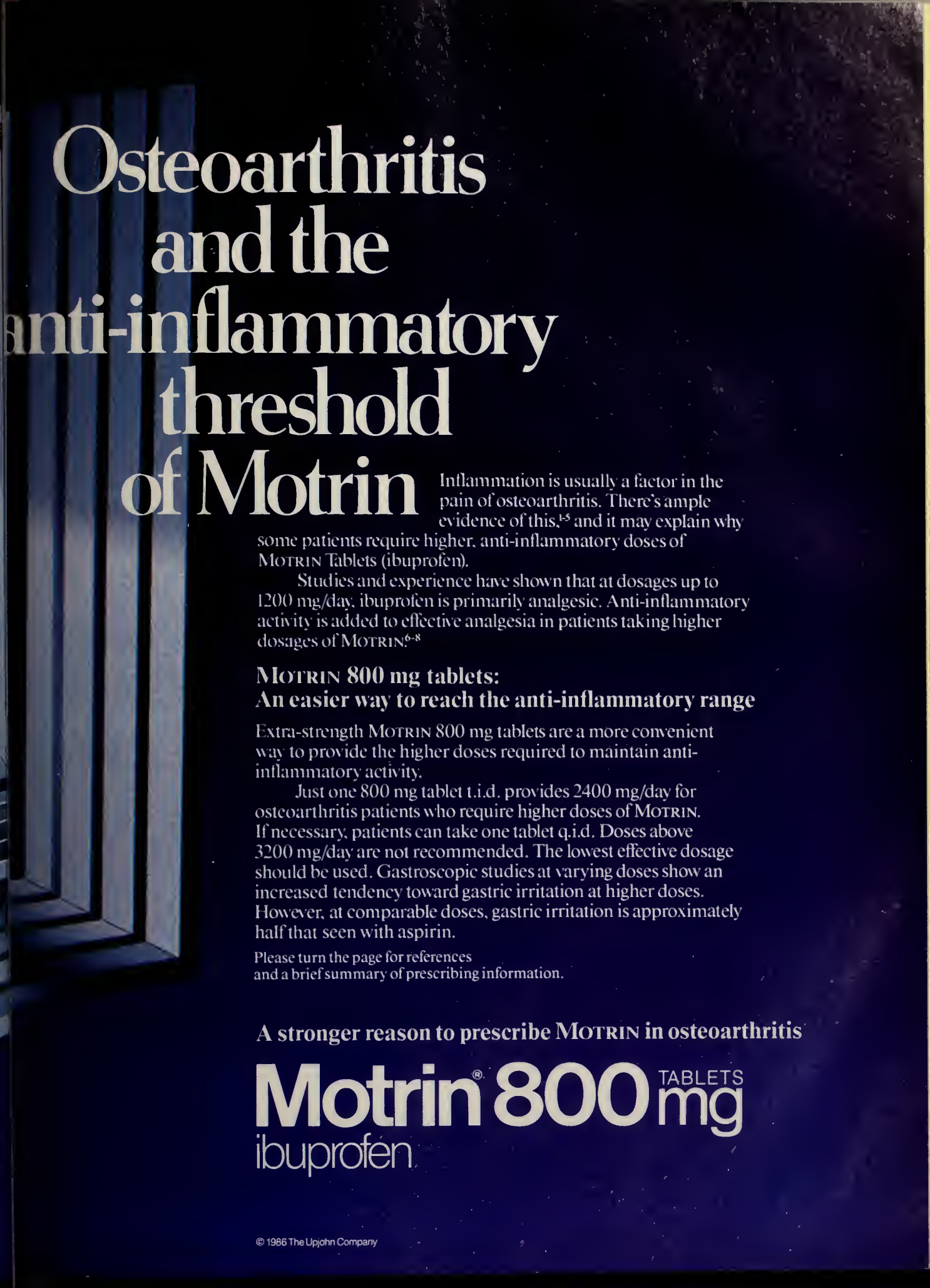

Osteoarthritis and the anti-inflammatory threshold of Motrin

Inflammation is usually a factor in the pain of osteoarthritis. There's ample evidence of this,[1-5] and it may explain why some patients require higher, anti-inflammatory doses of MOTRIN Tablets (ibuprofen).

Studies and experience have shown that at dosages up to 1200 mg/day, ibuprofen is primarily analgesic. Anti-inflammatory activity is added to effective analgesia in patients taking higher dosages of MOTRIN.[6-8]

MOTRIN 800 mg tablets: An easier way to reach the anti-inflammatory range

Extra-strength MOTRIN 800 mg tablets are a more convenient way to provide the higher doses required to maintain anti-inflammatory activity.

Just one 800 mg tablet t.i.d. provides 2400 mg/day for osteoarthritis patients who require higher doses of MOTRIN. If necessary, patients can take one tablet q.i.d. Doses above 3200 mg/day are not recommended. The lowest effective dosage should be used. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin.

Please turn the page for references and a brief summary of prescribing information.

A stronger reason to prescribe MOTRIN in osteoarthritis

Motrin® 800 mg TABLETS
ibuprofen

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For the inflammation and the pain of osteoarthritis

Motrin® 800 mg TABLETS
ibuprofen

A stronger reason to prescribe MOTRIN.

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MOTRIN® Tablets
(ibuprofen)

CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship**

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown**

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

HOW SUPPLIED:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
Bottles of 500	Bottles of 500	Bottles of 100
Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
Unit of Use bottles of 100	Unit of Use bottles of 100	

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

For additional product information, see your Upjohn representative or consult the package insert.

MED B-9-S

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February 1986
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C I B A

(See Brief Summary of Prescribing Information on the next page.)

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529-7750-A

Transderm-Nitro®
nitroglycerin
Transdermal Therapeutic System

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea and vomiting. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued. In some patients, dermatitis may occur.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.
The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.
The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.
Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
2.5 mg/24 hr	12.5 mg	5 cm^2	30 Systems (NDC 0083-2025-26) *100 Systems (NDC 0083-2025-30)
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26) *100 Systems (NDC 0083-2105-30)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26) *100 Systems (NDC 0083-2110-30)
15 mg/24 hr	75 mg	30 cm^2	30 Systems (NDC 0083-2115-26) *100 Systems (NDC 0083-2115-30)

*Hospital Pack 100's

C85-35 (Rev 11/85)

Dist. by:
CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

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C I B A

In Memoriam

California Medical Association

BARNES, JAMES P., Walnut Grove. Died May 21, 1987, aged 73. Graduate of University of Arkansas College of Medicine, Little Rock, 1940. Licensed in California in 1946. Dr Barnes was a member of the Sacramento-El Dorado Medical Society.

❧

CARDEY, NORMAN L., Died Apr 17, 1987, aged 77. Graduate of Loma Linda University School of Medicine, 1934. Licensed in California in 1946. Dr Cardey was a member of the Los Angeles County Medical Association.

❧

CARMACK, JAMES C. Died Apr 12, 1987, aged 90. Graduate of University of Texas, 1930. Licensed in California in 1931. Dr Carmack was a member of the San Bernardino County Medical Society.

❧

CERV, ERNEST A. Died May 1987, aged 74. Graduate of University of Nebraska College of Medicine, Omaha, 1940. Licensed in California in 1945. Dr Cerv was a member of the Los Angeles County Medical Association.

❧

CHATTERJEE, ALO, Merced. Died Apr 26, 1987, aged 43. Graduate of University of Calcutta, 1967. Licensed in California in 1975. Dr Chatterjee was a member of the Merced-Mariposa Medical Society.

❧

CHATTERJEE, CHITTA R., Merced. Died Apr 26, 1987, aged 51. Graduate of University of Calcutta, 1959. Licensed in California in 1975. Dr Chatterjee was a member of the Merced-Mariposa Medical Society.

❧

COY, L. PIERCE, San Mateo. Died May 30, 1987, aged 71. Graduate of Vanderbilt University School of Medicine, Nashville, Tenn, 1943. Licensed in California in 1946. Dr Coy was a member of the San Mateo County Medical Society.

❧

CRAY, G. CAMERON, Palo Alto. Died Apr 27, 1987, aged 64. Graduate of State University of New York Downstate Medical Center, Brooklyn, 1951. Licensed in California in 1952. Dr Cray was a member of the Santa Clara County Medical Society.

❧

ENGSTROM, ROBERT E. Died Apr 9, 1987, aged 57. Graduate of University of California, Irvine, 1962. Dr Engstrom was a member of the Los Angeles County Medical Association.

❧

FRANKLIN, ROLAND G., Murrieta. Died Apr 5, 1987, aged 72. Graduate of University of Southern California School of Medicine, Los Angeles, 1941. Licensed in California in 1941. Dr Franklin was a member of the Riverside County Medical Association.

❧

GARDINER, FREDERICK S. Died Feb 10, 1987, aged 73. Graduate of McGill University, Montreal, 1939. Licensed in California in 1947. Dr Gardiner was a member of the San Diego County Medical Society.

❧

GUCKER, THOMAS, III. Died Mar 31, 1987, aged 71. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1941. Licensed in California in 1958. Dr Gucker was a member of the Los Angeles County Medical Association.

JESSUP, ROBERT BRUCE, Palo Alto. Died June 2, 1987, aged 67. Graduate of Stanford University School of Medicine, 1949. Licensed in California in 1949. Dr Jessup was a member of the Santa Clara County Medical Society.

❧

KEARNEY, SANBORN G. Died Apr 5, 1987, aged 78. Graduate of University of California, 1935. Licensed in California in 1935. Dr Kearney was a member of the Kern County Medical Society.

❧

KOENIGSBERGER, ERNST. Died Apr 22, 1987, aged 92. Graduate of University of Leipzig, 1922. Licensed in California in 1942. Dr Koenigsberger was a member of the Alameda-Contra Costa Medical Association.

❧

LOIGNON, HENRI P., Port Hueneme. Died May 22, 1987, aged 58. Graduate of University of California, Irvine. Dr Loignon was a member of the Ventura County Medical Society.

❧

LOPES, JOHN D., Mountain View. Died May 23, 1987, aged 64. Graduate of Jefferson Medical College, Philadelphia, 1950. Licensed in California in 1951. Dr Lopes was a member of the Santa Clara County Medical Society.

❧

LUTZ, MICHAEL D. Died Mar 1987, aged 47. Graduate of University of North Carolina, Chapel Hill, 1968. Licensed in California in 1973. Dr Lutz was a member of the San Diego County Medical Society.

❧

MCCREA, FRANCIS R. Died Feb 27, 1987, aged 95. Graduate of Stanford University, 1925. Licensed in California in 1925. Dr McCrea was a member of the Los Angeles County Medical Association.

❧

MCGUIRE, FRANK A. Died Mar 3, 1987, aged 87. Graduate of University of Manitoba, Winnipeg, 1924. Dr McGuire was a member of the San Joaquin County Medical Society.

New Mexico Medical Society

ALHADEFF, NORMAN L., Albuquerque. Died Jun 11, 1987, aged 38. Graduate of Tufts University School of Medicine, Boston, 1979. Licensed in New Mexico in 1986. Dr Alhadeff was a member of the Greater Albuquerque Medical Association.

❧

BIVENS, MELVIN D., Albuquerque. Died Jun 3, 1987, aged 69. Graduate of University of Colorado School of Medicine, Denver, 1946. Licensed in New Mexico in 1953. Dr Bivens was a member of the Greater Albuquerque Medical Association.

❧

MIX, NANCY J., Albuquerque. Died Jun 11, 1987, aged 37. Graduate of Boston University School of Medicine, 1974. Licensed in New Mexico in 1986. Dr Mix was a member of the Greater Albuquerque Medical Association.

Utah State Medical Association

BUDGE, OLIVER W., Logan. Died May 19, 1987, aged 84. Graduate of Northwestern University Medical School, Chicago. Dr Budge was a member of the Cache Valley Medical Society.

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E. R. W. FOX, MD

Dr Fox is in private practice in Coeur d'Alene and is the Special Editor for Idaho.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 5-7—**Gynecologic Surgery: Principles, Techniques and Management of Complications.** Hyatt Regency, Scottsdale. Thurs-Sat. Contact: Robin Murray, ACOG, (202) 638-5577, ext 343.

November 16-17—**Update on Management of Spina Bifida.** La Posada Resort, Scottsdale. Mon-Tues. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800)-BARROW-1.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

August 23-28—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Royal Waikoloa Hotel, The Big Island, Hawaii. Sun-Fri. 20 hrs. $375. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 12-13—**Case Conference on Clinical Anesthesiology.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $160. Contact: California Society of Anesthesiologists, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

January 31-February 5—**Biennial Western Conference on Anesthesiology: 1988 Clinical Update in Anesthesiology.** Toussaint Hospital Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. 22.5 hrs. $375. Contact: Murray G. Atnikov, c/o Box F110-63, Baline, WA 98230. (604) 874-5291.

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Westin Maui, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiology, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

September 12—**Advances in Lung Cancer.** UCI at Long Beach. Sat. Contact: UCI.

September 19—**Third Annual Cancer Conference.** St. Agnes Medical Center at Total Life Center, St. Agnes Medical Center. Sat. 5 hrs. $35. Contact: Carol Witham, St. Agnes Medical Center, 1303 E Herndon Ave, Fresno 93710. (209) 449-3570.

October 19-21—**11th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 21 hrs. $350. Contact: Nomi Feldman, Scripps Memorial Hospital, 3770 Tansy, San Diego 92121. (619) 453-6222.

December 9—**23rd Northern California Cancer Conference.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th and The Esplanade, Chico 95926. (916) 891-7300.

December 12—**Bronchology Laser Cancer Symposium.** UCI at Long Beach. Sat. Contact: UCI.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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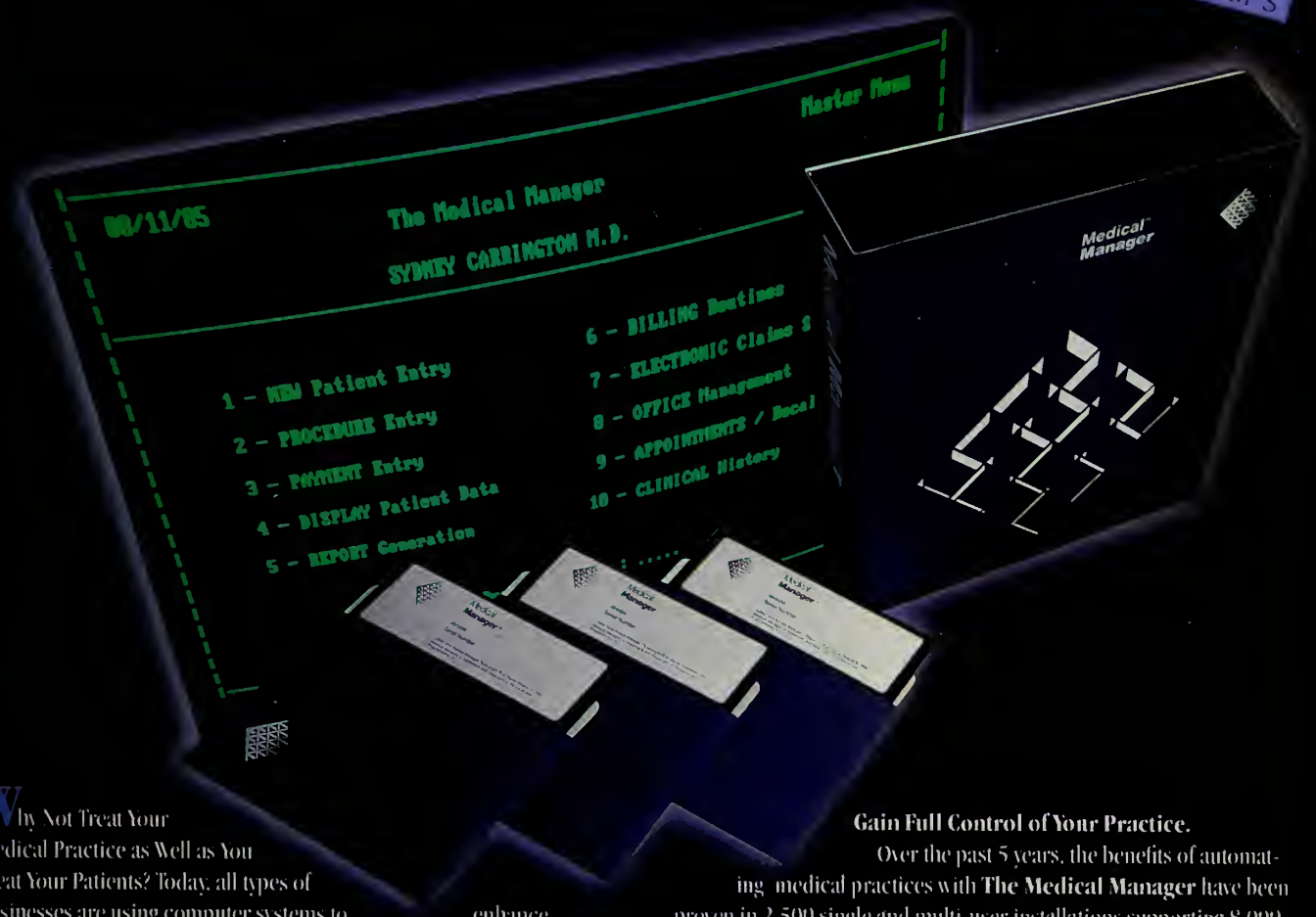

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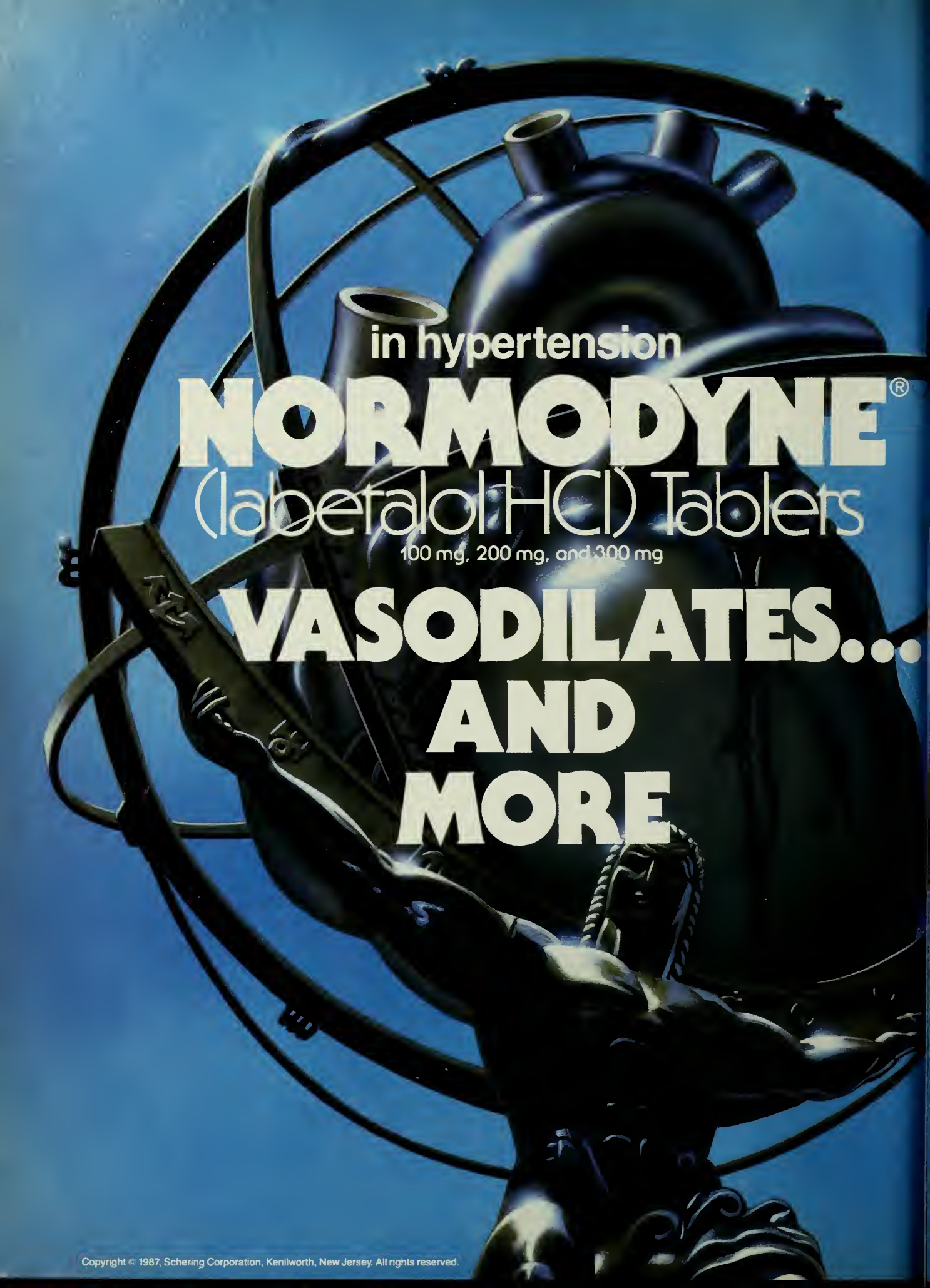

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Supports your patients' vital organs

- lowers blood pressure by reducing total peripheral resistance
- does not adversely affect heart rate and maintains cardiac output
- beta blockade minimizes risk of reflex tachycardia
- produces no adverse effect on HDL, cholesterol, or triglycerides
- does not impair renal function

...and supports your patients' life-styles

- maintains exercise capacity yet blunts surges in heart rate
- demonstrates a low incidence of impotence, fatigue, and cold extremities*

*Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) have occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

NORMODYNE®
(labetalol HCl) Tablets

For Brief Summary, please see following page.

13071942-JBS **PRODUCT INFORMATION**

NORMODYNE®

brand of labetalol hydrochloride

Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In *Patients Without a History of Cardiac Failure* In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see Drug Interactions).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4

Labetalol HCl Daily Dose (mg) (cont.)	800	900	1200	1600	2400
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See CONTRAINDICATIONS.

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: Excessive *bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a β_2-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

Schering Corporation
Kenilworth, NJ 07033

Revised 3/85

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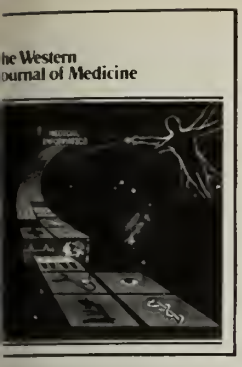
SPECIAL ISSUES



Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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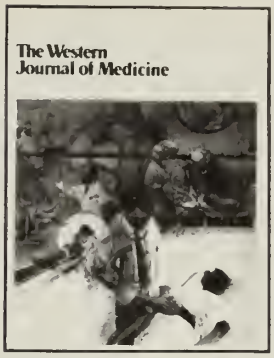

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

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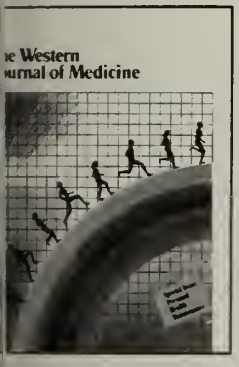

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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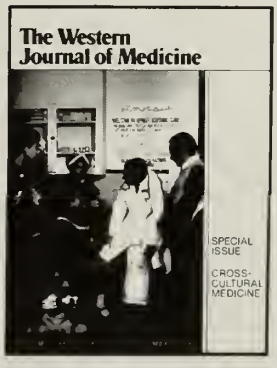

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The barriers may be great indeed when an American-trained physician undertakes to treat a patient from another ethnic or religious background. Too little attention has been given to developing better or even adequate communication across all these different cultures. The subject is of worldwide social, economic and political importance, and on a more individual and personal basis it is important in patient care.

—Malcolm S. M. Watts, MD

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Insulin levels are rapidly elevated in response to a meal, then return promptly to basal levels after the meal challenge subsides.

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Rapidly metabolized and excreted, with an excellent safety profile.[1] As with all sulfonylureas, hypoglycemia may occur.

In concert with diet in non-insulin-dependent diabetes mellitus

Glucotrol®

(glipizide) 5-mg and 10-mg Scored Tablets

SYNCHRONIZED SULFONYLUREA THERAPY

Please see brief summary of Glucotrol® (glipizide) prescribing information on next page.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

Reference
1. Sachs R, Frank M, Fishman SK: Overview of clinical experience with glipizide, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 163-172

GLUCOTROL® (glipizide) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 19, supp. 2:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutegenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C. GLUCOTROL (glipizide) was found to be mildly tetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas. GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NOC 5 mg 0049-4110-66) Bottles of 100, 10 mg tablet—Pfizer 412 (NOC 10 mg 0049-4120-66) Bottles of 100.

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

ROERIG Pfizer A division of Pfizer Pharmaceuticals New York, New York 10017

CONTINUING MEDICAL EDUCATION

(Continued from Page 142)

CARDIOLOGY

September 11-13—**Advanced Cardiac Life Support.** CPR Seminars at Incline Village, Lake Tahoe, Nevada. Fri-Sun. $170. Contact: CPR Seminar, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

September 12—**57th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Association, San Francisco at Cathedral Hill Hotel, San Francisco. Sat. 9 hrs. $100. Contact: AHA, 42 Powell St, San Francisco 94102. (415) 433-2273

September 17-18—**Optimal Coronary Revascularization.** Santa Barbara Medical Foundation Clinic, Sansum Medical Clinic and Santa Barbara Cottage Hospital at Red Lion Resort Hotel, Santa Barbara. Thurs-Fri. 14 hrs. $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sun. 13 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

September 25-27—**International Workshop on Future Directions in Interventional Cardiology.** American College of Cardiology at Red Lion Resort, Santa Barbara. Fri-Sun. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (800) 253-4636, ext 226, or (301) 897-5400.

October 15-17—**11th Annual Seminar: Cardiology Update 1987.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

October 15-17—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 30-31—**Coronary Heart Disease.** Medical Education Resources at Las Vegas Hilton Hotel, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 13-14—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hilton Hotel, San Francisco. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 14—**16th Annual Cardiology Symposium.** Fresno Community Hospital at Center Plaza Hotel, Fresno. Sat. Contact: Joann Ellis, Fresno Community Hospital, PO Box 1232, Fresno 93715. (209) 442-3936.

December 4-5—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

January 22-24—**Advanced Cardiac Life Support,** CPR Seminars at Ralph K. Davies Medical Center. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 28-30—**Clinical Nuclear Cardiology.** ACC at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. Contact: Mary Anne McIneny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

DERMATOLOGY

October 24-25—**16th Annual Mycology Review.** STAN at STAN. Sat-Sun. Contact: STAN.

EMERGENCY MEDICINE

August 21-23—**Sports Medicine Updates.** J. Bear Co at Klamath River (whitewater rafting). Fri-Sun. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 31-September 4—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

September 5-7—**Wilderness Medicine.** J. Bear Co at Klamath River (whitewater rafting). Sat-Mon. 10 hrs. $295. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 150)

September 11-13—**Advanced Cardiac Life Support.** CPR Seminars at Incline Village, Lake Tahoe, Nevada. Fri-Sun. $170. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

September 13-20—**Diving and Marine Medicine.** J. Bear Co at Lahaina, Maui, Hawaii. One week. 10 hrs. $850. Contact: J. Bear Co, PO Box 1536, Yreka 96097. (916) 842-6970.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550.

INTERNAL MEDICINE

August 23-28—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $395. Contact: UCD.

October 10—**Clinical Update on Thromboembolic Disease and Anticoagulation.** UCD at Hilton Hotel, Sacramento. Sat. Contact: UCD.

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

November 11—**Gastroenterology.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

OB/GYN

September 19-22—**The Fetus and Newborn.** Contemporary Forums at San Diego. Sat-Tues. Contact: Contemporary Forums, 530 La Gonda Way, Ste E, Danville 94526. (415) 820-2800.

October 16-18—**Advanced Fetal Heart Rate Monitoring.** UCI at Embassy Suites Hotel, Napa Valley. Fri-Sun. Contact: UCI.

November 15-21—**10th Annual Review Course in Clinical Obstetrics & Gynecology and/or Gynecological Histopathology** at UCI. Sun-Sat. Contact: UCI.

December 4-5—**Environmental Exposure and Fetal Development (March of Dimes).** UCD at Sacramento Inn. Fri-Sat. Contact: UCD.

OPHTHALMOLOGY

August 30-Sept 2—**Under Pressure: Glaucoma 1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. 12 hrs. $325. Contact: UCD.

December 10-11—**Ophthalmic Plastic and Reconstructive Surgery: Past, Present, and Future—A Tribute to Crowell Beard, MD.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

PATHOLOGY

August 22-29—**7th Annual Symposium on Fine Needle Aspiration.** California Society of Pathologists and UCSF at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. One week. 24.5 hrs. Contact: UCSF.

October 3—**Fine Needle Aspiration Tutorial.** UCSF at UCSF. Sat. 7 hrs. $475. Contact: UCSF.

(Continued on Page 155)

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Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. For complete prescribing information, please see package insert.

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CONTINUING MEDICAL EDUCATION

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PEDIATRICS

September 12-13—**44th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sheraton Universal Hotel, Los Angeles. Sat-Sun. Contact: Los Angeles Pediatric Society, PO Box 9022, Inglewood 90305. (213) 757-1198.

October 10-17—**11th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea Beach, Hawaii. One week. Contact: UCI.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 16-18—**Current Advances in Pediatrics.** American Academy of Pediatrics and UCI at Disneyland Hotel, Anaheim. Fri-Sun. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

October 23-25—**Current Concepts in Pediatric Gastroenterology.** Children's Hospital, Oakland at Doubletree Hotel, Monerey. Fri-Sun. Contact: Kim Leadon, CME Office, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

November 20-23—**9th Annual Las Vegas Seminars—Pediatric Update.** Los Angeles Pediatric Society at Caesar's Palace. Fri-Mon. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

PSYCHIATRY

October 17-18—**Dynamics of Human Development—Implications for Treatment.** Continuing Education Seminars at Los Angeles. Sat-Sun. 11.5 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave, Los Angeles 90024. (213) 475-8300.

November 6-8—**33rd Annual: Group Therapy Symposium.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

August 22-29—**Radiology.** USC at Maui Marriott Hotel, Maui, Hawaii. One week. 26 hrs. $525. Contact: USC.

August 26-28—**Interventional Radiology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. Contact: UCSF.

August 27-30—**3rd Annual Physics and Biology of Radiology.** UCSD at San Diego Town and Country Hotel. Thurs-Sun. 26.5 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 28-30—**3rd Annual Sonographers' Update and Review.** UCSD at Bahia Resort Hotel, San Diego. Fri-Sun. 16 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 29-30—**Advances in Imaging Technology.** UCSF at Hyatt Regency, San Francisco. Sat-Sun. Contact: UCSF.

September 10-12—**Contemporary Diagnostic Imaging: CT, Interventional, MRI, US.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

September 10-12—**Advances in Sectional Imaging.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 14 hrs. $375. Contact: UCSD.

September 10-13—**Physics of Diagnostic Radiology.** UCD at UCD. Thurs-Sun. 25 hrs. Contact: UCD.

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Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*

Warnings: ***Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.*** *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*

Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosoria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*

Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*

Supplied: ***'Dyazide' is supplied as a red and white capsule in bottles of 1DDD capsules; Single Unit Packages (unit-dose) of 1DD (intended for institutional use only); In Patient-Pak™ unit-of-use bottles of 1DD.***

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

AUGUST 1987, VOL. XLIV, NO. 8

"You Diagnosed Me, But You Wouldn't Treat Me"

Marshall B. Block, M.D.

Several years ago during one of my parents' treks to Arizona from their retirement home in Florida, I was taken aback by my mother's appearance as they arrived at the airport. She'd gained about 20 pounds, looked bloated and had a somewhat yellow cast to her skin. Her voice was husky and her eyes were a bit puffy. After the usual hugs and kisses and their ultimate settlement in the local motel, I pulled my mother aside and asked her whether she had noticed any physical changes. She related a history compatible with hypothyroidism and I suggested that she contact her physician when she returned home to be checked for that disorder. A month passed after their return to Miami without a word from my mother. I decided I had better call and find out what transpired. She was rather cool on the phone and when questioned further I discovered that she was "angry with me." "Why?" I asked. (I was thinking that she should have been proud of me for having made the correct diagnosis, but I was wrong again.) "You diagnosed me correctly, but you didn't treat me." I thought long and hard about her response, and although I was initially disappointed, I think she was describing a common malady.

We very often in our busy schedules enjoy the challenge of making a diagnosis. Somehow the uncertainty, the mystery, the intrigue of the search is what makes medicine so exciting on a day to day basis. Whether one operates and is searching for a parathyroid adenoma, or one is trying to dig out a splinter from a finger in the emergency room, or one is taking a lengthy history from a patient with bizarre symptomatology, each is attempting to find a solution to a problem. Finding an adenoma, finding and removing the splinter, and coming to the correct diagnosis is the reward. The hunt is what makes it all worthwile for many of us, and for some of us, myself included, we sometimes lose sight that to the patient the hunt is really just the beginning. Once the problem is found, there are ramifications that in some instances are long-lasting. Solutions include lifestyle changes, the taking of medications, surgery, and follow-up appointments. All of these produce a burden for the patient. We on occasion don't realize the importance of these changes and tend to be somewhat cavalier in prescribing them. Although it is relaxing to know a patient well, including details of their family and social circumstances, for some it is not as rewarding as the constant challenge of the unknown. Many of us place greater emphasis on the search than on the follow-up.

It was more important for my mother to be "treated" than to be diagnosed. Treatment implies a change of some sort, whether it be a diet, a pill, or surgery. It is seen as an active involvement by the physician in the patient's care. A bond develops in this therapeutic process which links patient to physician and fosters a more per-

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

AUGUST 1987, VOL. XLIV, NO. 8

Arizona Medicine is a socioeconomic and scientific journal published monthly by The Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine.* All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by The Arizona Medical Association.

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  Louis J. Kettel, M.D.
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ArMA's New Young Physicians Section

Across the nation — including Arizona — young physicians are staying away from organized medicine in droves.

Some fail to see "what's in it for them" to spend the energy to join and participate. Others feel professional medical organizations are for older established physicians, not for them. Still others simply are unable to spend the time or the money to join.

Whatever the reason for their reluctance, their failure to play an active role in organized medicine constitutes a threat to the continuing quality of professional health care.

The future of American medicine lies in the hands of its young physicians, so it is critically important for them to link their hands in an organized effort to preserve and protect their ability to deliver quality medical care. Someone has to get to America's young physicians and let them know that participating in their professional medical organizations yields both short-term and long-term benefits of direct interest to them as individuals and as medical professionals.

That's the premise behind the establishment of Young Physicians Sections in the American Medical Association and in state medical associations around the nation. It is the basis for the establishment of ArMA's Young Physicians Section.

"We need to be unified to have effectiveness," says Young Physicians chairman Jacqueline Chadwick, M.D. "We cannot as individuals do what we can do together."

Together, young physicians can reap the benefits of group programs sponsored by the state professional association, such as ArMA's financial, insurance and pension programs.

When you go into practice, you are bombarded with many, many contacts from people offering deals on all kinds of professional services," Dr. Chadwick said, "and sometimes it's difficult for a young physician to know which one is best, which one can be trusted to do the best work for you. Now that ArMA is offering these programs, we don't have to worry anymore whether the people offering these services will work in our best interest. That's an instant benefit."

But more important is the long-term benefit which comes from people working together to protect their professional standards.

"What all doctors care about," she said, "the bottom-line goal, is delivering quality medical care. They want to be good doctors. Organized medicine helps attain that goal, and we have to show young physicians that they are an important part of that process."

Continued on page 16

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Barrow Neurological Institute Founder Retires

John Green, M.D.

(Editor's note:) John Green, M.D., founder and chief administrator of Barrow Neurological Institute, Phoenix, retired in June following a truly outstanding medical career. This is one look at his story.)

There was a time when John Green thought he could know it all ..... that if he just worked hard enough, studied enough, learned enough, he really would understand all there was about the human brain and its interactions with man's other physical functions.

But that was forty-odd years ago, when Dr. Green was fresh out of Northwestern University Medical School and most of today's commonplace technologies were medical marvels yet undiscovered. It didn't take long for him to realize his expectation was impossible, to see that no one man, no matter how brilliant, could ever know all there is to know about his brain. So Dr. Green built Barrow Neurological Institute (BNI) to do it for him.

"That's what an institute is," he observes, "a collection of people who together can find the answers and do things that no one man could find or do alone"

Finding answers—and sharing them with successive new generations of physicians-in-training — is what Barrow is all about. There always will be new things to learn, new discoveries to make. But in terms of comprehensively encompassing virtually all extant knowledge of the "neuros" — neurology, neurosurgery, neurobiology, neurochemistry, neurophysiology, neuropsychiatry, neuroradiology, et. al — Barrow is as good as they come. There aren't ten other institutes in North America which are its peers.

And that's not a bad life's accomplishment, especially considering they said it never could be done.

Arizona was a desert, medically as well as meteorologically, in the days before BNI. There just wasn't anything in the Southwest that approximated sophistication in neurological research or technology. And there didn't seem to be much of a market for it, either.

Charles Barrow's attorneys told him not to get involved in such an idealistic and unrealistic project. They said it was a bad investment, one which would never succeed.

But Barrow hadn't achieved his phenomenal business success by letting his attorneys bully him. He wasn't used to taking "no" for an answer, and he was determined to do something for the brilliant young neurosurgeon who'd taken such good care of his beloved wife. So Charles Barrow defied his lawyers and put up half a million dollars in the late 1950s. That enabled Dr. Green and Sister Placida to build his dream, and Barrow Neurological Institute was born.

Sister Placida was "the truly remarkable administrator" of St. Joseph's Hospital at the time, which was the "only hospital in Phoenix which had training programs in all the specialties, and which also did charity work," Dr. Green recalls. "It seemed the best environment for an academic institute."

He thought about enlisting Arizona State Hospital, where he had worked with mental patients since his arrival in Phoenix in 1947. But the state facility would not have included private patients, which Dr. Green considered essential to the success of a comprehensive neurological institute. So he looked over the private

hospital market and chose St. Joseph's as his partner.

Sister Placida convinced the hospital board to give 100 percent support to the neurological institute, persuading them it would be a great asset. The hospital's ongoing — and already funded — renovation plan included $875,000 which helped provide space for the fledgling institute. An additional $500,000 in matching money was solicited from federal Hill-Burton funds. Charles Barrow donated additional funds as the institute grew, ultimately giving $1.3 million toward the development of the institute.

In order to be successful, Dr. Green said, the institute had to do three things extremely well. First, it had to provide the most sophisticated patient care available; then it had to maintain its progressive knowledge with an intensive research program; and finally, it had to share its knowledge with the next generation of physicians through a comprehensive academic training program.

"The sisters were responsible for teaching patient care," Dr. Green said, "but research was something new and had to be provided. It made the institute effective, and sets a different tone to the staff."

In order to establish the research component, Dr. Green wrote 100 letters to various people he knew around Arizona who he felt might be able to help establish a research budget. The letter campaign was effective — one still anonymous former patient donated $2 million to the cause.

Just as he reached out to develop the research component, Dr. Green reached out, this time across the continent, to establish the most progressive and talented staff which could be gathered. Today, there are 19 neurosurgeons on the Barrow staff, most of whom are "really world class," Dr. Green says. Additionally, they have a resident training staff, an annual operative load of over 1,000 cases, and a growing international reputation for neuroscientific research.

But what leads a man down his chosen path? What drew Dr. Green toward neurosurgery in the first place?

It's who you've known, he says, the influence of others. While he was in medical school, one dynamic professor taught anatomy and the young John Green found the nervous system "fascinating."

But he did'nt make the decision to specialize until his residency and fellowship at the Illinois Neurological Institute with Eric Oldberg, M.D., who had had *his* training with the father of neurosurgery, the legendary physician Harvey Cushing. Dr. Oldberg was well on his way toward becoming a legend in his own right, and colleagues on the teaching staff included the master surgeon-teachers Percival Bailey and Paul Bucy. Considering the influence of this outstanding trio, it is no wonder the young medical student fell under the spell of their neural magic.

Asked why he came to Phoenix and worked so hard to establish a facility like BNI, Dr. Green was blunt and brief. "I thought they trained me for something (important)," Dr. Green said, implying that his success in establishing BNI is no more than he owed his magnificent mentors. ■

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In today's highly competitive medical marketplace, it is quite surprising to still speak with physicians who are unaware of the fact that their practices have a value as a business independent of the physician. Over the past five years, we have seen a steady increase in the number of practices being sold to other physicians. Further, we have also witnessed an increasing number of hospitals purchasing practices in the State of Arizona. Hospitals are purchasing practices to assure themselves of patient admissions, but many senior physicians are asking, "Why would another doctor or group of doctors be interested in purchasing my practice?"

The two fundamental reasons why we are witnessing an increasing number of medical practices being bought and sold is due to:

1. The cost of capital involved in trying to establish a new practice. It is not unusual to find new primary care specialists incurring debts up to $100,000 prior to reaching a break-even point in their practice operations. Specialists such as otolaryngologists and ophthalmologists can see their initial costs escalate even higher, due to the expensive equipment they have to purchase for their practices.

2. The sheer number of doctors entering practice each year, currently estimated at 16,000, is making established practices realize that the advent of new competition will divide the patient pie into smaller and smaller pieces. Consequently, we are beginning to see the development of practice mergers, and outright purchases of small practices by larger practices to preclude any additional competition entering the community.

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Richard E. Kirkpatrick

There are six major reasons why a medical practice would be made available for purchase:

1. *Recruiting* a new associate and offering that individual a portion of the practice's assets;

2. *Retirement* of a physician either from solo practice or from group practice who wishes to sell his share in the practice to his colleagues or to a new or established community physician;

3. *Permanent physician disability*- may force a doctor to consider the sale of his practice to aid the funding of his living standard due to a permanent disability;

4. *The death of a doctor* will usually force a spouse or partners to consider the importance of a practice valuation in order to determine the practice's value for sale to another physician or to the departed doctor's partners.

5. *A doctor's divorce,* at this time, will always force a practice valuation as a part of the adjudication and support payment process for the ex-spouse.

6. *Infrequently, a move may be made by a physician* from one community or state to another. The motivations for such a move can be viewed in any of the five reasons listed above, or could be related to the doctor being named in significant malpractice suits.

Assessing the value of a practice is an involved and detailed process. There are three methods for determining the value of a practice:

1. The market data method, in which the practice is compared with other similar practices in terms of revenue, expenses, and profitability before and after physician compensation.

(Next pg.)

2. The discounted future earnings method. This technical approach involves the estimation of future income before and after physician compensation based on historical data.

3. The adjusted equity method is based primarily on the underlying value of the assets which brings all real estate, equipment and other items of both tangible and intangible value to a fair market value. This is a rather difficult one to use in medicine, since, in most cases the value of the equipment may be negligible, and the real estate may be owned by a totally separate entity.

In determining a value of a practice, there are several major items which must be taken into consideration:

A. Profit.
B. Potential growth.
C. The physical facilities.
D. The services.
E. The personnel.

The accounts receivable of a practice should be excluded from any part of the transaction in the case of an outright sale or merger. The doctor who owned the practice or the group who owned the practice should collect their own accounts receivable, with the new accounts receivable being determined from the first day of ownership of the new entity. The evaluation of most of the hardware is fairly straight forward based on its depreciated value, its market value, or its replacement value. Determination of "goodwill" is much more open to question. There are numerous proposals and articles written which purport to state that goodwill is always worth a portion of the practice's annual revenues. This may, in fact, be the case, but there is no such thing as a standard percentage of revenue which can be utilized in all cases for the determinaiton of goodwill value.

From a technical point of view, the most common technique for determining the goodwill value of a practice is the IRS method, also referred to as the capitalized value of excess earnings. With this technique, the practice's value is determined based on the amount of excess earnings it generates compared to the earnings of other practices. In the case of medical practices, the most sensible technique to be utilized is this one in combination with a comparison with other practices in the same specialty in the same community. It is very difficult, if not impossible, to compare national figures with the local environment. This is particularly true in the case of Phoenix, where physicians, generally speaking, generate more income than their colleagues in other parts of the country. This tends to depreciate the value of goodwill in a practice as a consequence. An example of this process is illustrated below:

Annual profits	**$ 450,000**
Tangible assest	**3,500,000**
Expected rate of return on investment	**10%**
Multiply	**3,500,000 x 10%**
Expected return	**350,000**
Actual profit "Normal" profit	**450,000 - 350,000**
"Excess" profit	**100,000**
Divide excess profit by required rate of return	**100,000 Divided by 20%**
PRACTICE GOODWILL	**500,000**
Practice goodwill	**500,000**
Add to tangible assets	**+ 3,500,000**
Total practice value	**$ 4,000,000**

When selling or buying a practice or any share of a practice, it is absolutely essential that written documentation be developed outlining the rights and obligations of the parties involved. We have seen too many excellent endeavors come to a terrible end due to misunderstandings over "gentlemen's agreements" and, in too many situations, the ladies and gentlemen involved have differing memories concerning what was discussed and what was agreed upon. For each party's own protection, it is essential that the understanding between the parties be documented in writing, outlining the procedures for the sale and purchase of a practice, or an interest in a practice.

The question might well be asked, how does one let other practitioners know that a practice

is for sale? The most common technique for the sale of a medical practice has been the word of mouth network. By simply allowing physicians on the hospital medical staff or within the medical community know that a practice is for sale, buyers will normally be forthcoming. A second method is to approach hospitals or health maintenance organizations directly with a proposal to sell. Such communications are normally handled by letter or telephone. It will be necessary to have a plan developed illustrating all of the attributes of the practice and its selling price prior to approaching any purchasing entity. Advertising generally generates calls from brokers.

When should a practitioner or group consider selling a practice? While the answer might be anytime, there are several situations in which speed of sale is of the essence. The two most significant situations are in the case of a doctor's death or disability. After a doctor has died or is permanently disabled, the practice's value deteriorates at an incredible rate of speed. Patients will begin seeking care elsewhere, and referring physicians will begin locating new specialists for their patients. Consequently, it behooves the doctor or the spouse to make an effort to sell the practice within six weeks of the date of death or disability in order to obtain the highest possible price for the practice. Aside from these two situations, the practitioner has a tremendous amount of flexibility in terms of the timing of the sale. The more time the practitioner has available to decide on offers, the less likely he or she will accept an inadequate offer. Consequently, some advanced planning is strongly recommended relative to the sale of a medical practice. Buy-ins, retirement, and similar items should be discussed with junior associates well in advance of the dates of these occurrences. This can avoid a significant amount of ill feeling in the long run.

Many group practices (nationally) have adopted a policy of periodic (every three to five years) valuations to determine practice value. This type of planning reduces group conflict and settles disputes much more quickly than an adversarial approach, at the time of sale. ■

Harold Toback, CPA
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Passive-Aggressive

First of a Series

William B. McGrath, M.D.

The passive-aggressive personality disorder is the one in which hostility or opposition is expressed only by indirect or covert means. Perhaps the individual grew up in an intimidating atmosphere and was seldom invited or permitted to disagree.

The disorder is rather common; so common in fact that it often goes unrecognized. This just compounds the frustration of the person who is trying to complete a transaction with a passive-aggressive. The disorder becomes a kind of blight: nothing quite comes to fruition.

A surgeon was a skilled handyman around the house and even in the kitchen. Anything his wife would attempt to do, he could do better, and she was constantly goaded with the fact. The more exasperated he became, the more inadequately she functioned. She finally took up drinking, even before breakfast, and soon she rendered herself too addled and clumsy to fix a meal or do the housework or groom herself properly for any social activity.

This was her way of conveying: "See what your ceaseless carping has done to me!" A one-dimensional diagnosis of alcoholism would obviously miss the point. As a matter of fact since their divorce she has never taken another drink.

A banker's younger brother is notorious for his sarcasm. He is smart enough to understand how he alienates people. Still his good intentions cannot stand up against his underhanded swordsmanship, and he leaves behind a trash container full of punctured egos and empty scrota.

A bright acquaintance tactfully pleaded with his wife to undertake some non-domestic activity or else share one or another of his wide-ranging interests. From then on she never started her tedious houshold chores until evening. When he desired bedtime intimacy, she tarried in the bathroom for an hour or so, taking her shower, painstakingly redoing her nails and her pedicure, pausing to glance through a brochure or a romance novel.

When he comes home from business trips he has to pick up the yellowing newspapers in the driveway. Once he won a tournament. Neither she nor any member of her family has ever mentioned it.

At a banquet her table companion listened attentively to a lecture or took part in a spirited discussion. Some inane remark of hers would distract him. She would go on murmuring in a voice so nearly inaudible that he would have to lean toward her, asking her to repeat herself. One time her husband suggested that they might repay another couple's hospitality with an invitation to dinner. She nodded, "One of these days," and that was eight years ago.

She is the one who usually keeps people waiting, and she seems almost proud of the fact. In an airport cafe the others were hurried by an announced departure of their flight. She insisted on ordering dessert.

If—and only if—you are finally prodded into protesting, you may evoke an apology—of sorts. "I am sorry to have seemed rude but it was entirely unintentional." See? She just "seemed" rude. So it must have been your fault for misinterpreting or over-reacting. In dealing with the passive-aggressive you will invariably end up being forgiven.

The passive-aggressive disorder is understandable (but *not* inevitable) in a younger sibling. Big brother still has some of the advantages of primogeniture. The arrival of the firstborn was thrilling in itself. He also embodied tangible hope for the marriage of the parents: something new and utterly fascinating that they now have in common.

Younger brother may not feel quite as wholeheartedly welcome. By then the mother and father

will have lost any illusions that offspring might solve their problems or really enrich what is left of their own relationship. Secondly, younger brother is invading occupied territory. He survives only with the ambivalent tolerance of firstborn.

Hence in formative years younger sibling does not compete on even terms, nor can he afford to put forth his best effort, lest by winning he might provoke a Cain-Abel rivalry.

Later, without remembering why, he will seem to steer clear of the more aggressive and competitive occupations. In the shoals of household relationships he could not just be himself. He may never measure up to his potential, and people will say of him: He never seemed to find himself.

Since he cannot securely be inner-directed, as the sociologists put it, he needs approval and especially permission from others. With companions (big brothers) he can venture into recreational and other situations which by himself he would avoid.

A few passive-aggressives are fortunate enough to be creative. They figuratively rebuild the world with sunnier and more open architecture. First, though, they have to chip away at the older structure with chisels of irony and disparagement.

Displacements occur, too. A neighbor is showering his little boy with all the exclusive attention and approval of which he felt deprived. His almost irrational defensiveness about this is a clue that there are unconscious determinants.

Executives and professional men tend to be rather assertive (else we wouldn't be here). Our authoritarian attitudes and intimidating ways might appear to be engendering or inflicting the passive-aggressive disorder. However the disorder itself has its roots in puberty.

We putative experts have been hung up too long on the sexual implications of a Freudian latency period. No! That decade, say from three to thirteen, is when a child learns that his behavior has consequences—but only for himself.

To perceive this pervasive self-centeredness is of paramount importance. For it is the underpinning of all the personality disorders, no matter how they otherwise diverge.

We hear with a puzzled frown the perennial hue and cry about sex education and the prevention of drug and alcohol dependencies. But ignorance of such disorders as the passive-aggressive is much more harmful. These problems should be identified in puberty while the personality is still pliable. Their recognition and redirection would prevent a hundred times more misery than any that result from sexual or chemical ignorance.

Enlightened guidance out of the egocentricity of the latency period is the duty of the concerned parent, with the help of physicians, clergymen, teachers.

Of lifetime helpfulness it would be for ten or twelve year olds to be given lots of hypothetical examples of behavior which is typical of this or that personality disorder. The youngster would soon recognize constellations of traits which are diagnostic. In our passive-aggressive, for example, these would be stubbornness, procrastination, obstructionism, questionable forgetfulness, inexplicable inefficiencies, habitual tardiness, pouting, and sweetly "innocent" sabotage.

The child could then apply this knowledge to himself and to those around him, but with a sprinkling of salutary mirth. Such is the beginning of wisdom.

Maturity will come later, when the individual appreciates that his behavior has consequences not only for himself but for others, and when example will have taught him to care. ■

William B. McGrath, M.D.

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Raindrops, Shock-Waves and Urinary Stones

What do raindrops have to do with shock waves and urinary stones? They represent the beginning of the space program research that led to the development of extracorporeal shock-wave lithotripsy, or the fragmentation of kidney stones without any surgical incision.

Space vehicles do not take off or land in rainstorms because the raindrops of the storm cause chipping of the windshields of the space vehicles. Dornier Company of West Germany was given the task of finding out why this occurred. Their first experiments were carried out with windshields mounted on the rocket sleds of White Sands Test Range in New Mexico. The engineers involved found that as the sleds moved through an artificial rainstorm at 2000 mph, each raindrop accelerated instantly from 0 to 2000 mph as it struck the windshields. Its weight was not enough to chip the windshield, but the miniature sonic boom created by passing through the sound barrier did have enough energy to chip the glass (or as was subsequently found, any crystalline substance).

As is often the case, the engineers studied the process carefully and determined that small amounts of shock-wave energy could chip almost any crystalline substance. They also found that putting a flexible rubber shield in the path of the shock wave did not alter it significantly, but that styrofoam or airbags stopped it completely. Then came the idea — could such waves be sent through the flexible body wall to chip away at gallbladder or kidney stones and turn them to sand? Laboratory and animal research began in West Germany in 1974. The first human was treated in Germany in February, 1980, and several additional treatments were reported in the medical journal, *Lancet* in 1981.

Kidney stones occur in Arizona at a rate 2.5 times higher than the national average, and we have had an ongoing research program in urinary stone disease since 1970. We immediately began to try to find out more about this new technology, now named extracorporeal shock-wave lithotripsy or ESWL (from the Greek lithos or stone, and tribien, to rub).

Arizona's first ESWL machine was installed in St. Joseph's Hospital, Phoenix, in May 1985. For nearly a year, Tucson urologists traveled with their patients to Phoenix in order to provide ESWL therapy. Finally, in May 1986, our own University Medical Center Lithotripsy Unit opened. Its facilities were made available to all Southern Arizona urologists who had accomplished the required training program. In the first year of operation, we treated 422 patients, which was slightly more than the number predicted at the time that the unit opened. As a segment of the urinary stone investigation program, this addition completed our program of basic laboratory research, clinical evaluation of patients to determine the cause of stones, and modern non-invasive surgical treatment of stones.

But even more investigative work in ESWL technology began at the University of Arizona College of Medicine with the installation of a laboratory ESWL unit in October, 1987. This is one of only three in the United States, and allows us to investigate the effects of ESWL on the skin, kidney, muscle and other tissues and stones. New uses for ESWL, such as destruction of tissue calcium, are under investigation. This new energy source, the shock-wave, the cause of windshield chipping in space craft, has been harnessed for use in medicine. Many innovative applications await us in the future. ■

George W. Drach, M.D.
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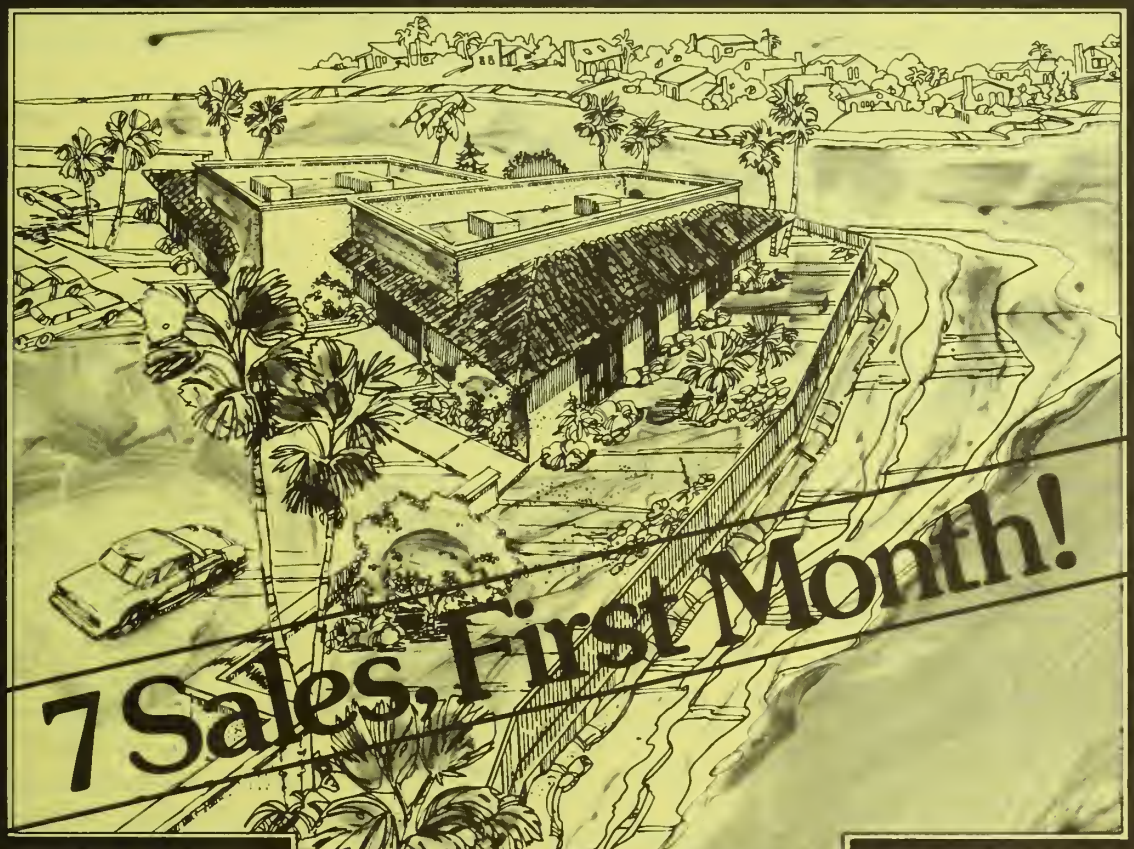

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Young Physicians Section *(Continued from page 2)*

Jacqueline Chadwick, M.D.

"For the Section to be successful, we have to be representative, we have to listen and be open to ideas from our members. We have to maintain an open door."

Lobbying, the process of influencing government decisions and legislation, and taking unified stands to the public, is most effective when done by an organization that represents all members who are going to be around for a long time.

Membership and interest in the Young Physicians Section, which was only begun to be organized last year, is growing — but has a long way to go, Dr. Chadwick said.

"We know from a survey we conducted that there's a lot of interest out there," she said. "The turnout at the meetings we've held has not been as great as we hoped. But the people who have showed up at our meetings have been enthusiastic, and have indicated that what we're doing and offering is exactly what young physicians need. I believe it's just a matter of time for the word to get around, for people to talk with each other, before the response will be everything we expect."

In order to encourage the broadest possible response from young physicians, the section meetings are open to both ArMA members and non-members.

"Our game plan is to work toward our goals, to see what we can do to represent the particular needs of young physicians, and to see how we can organize as a group to influence the broad picture."

"Our game plan is to work toward our goals, to see what we can do."

Arizona's Young Physicians Section was organized enough, early enough to serve as a model for the nation. The AMA established its Young Physicians Section in 1986 and at that time encouraged the states to follow suit. The first AMA meeting attended by Young Physicians Sections delegates was in Las Vegas last December.

"I believe it's just a matter of time for the word to get around."

"Our delegate, Jack Weiss was there," Dr. Chadwick said. "We were one of the few sections which had already adopted bylaws, and our bylaws were used as the basis for other Sections' bylaws across the country."

The Section's Governing Council recognizes that the demographics of young physicians are different from the demographics of older physicians. Younger physicians include more women and more employed physicians and more minorities than older groups, and they have a unique set of needs and concerns.

"For the Section to be successful, we have to be representative," Dr. Chadwick said. "We have to listen and be open to ideas from our members. We have to maintain an open door."

Members of the 1987-88 Governing Council include Dr. Chadwick; Tucson family practitioner Dennis Thrasher, M.D., Vice Chairman; and Phoenix otolaryngologist David Nielsen, M.D., Secretary. Other council members are Scottsdale otolaryngologist Jack Weiss, M.D., AMA Delegate; Phoenix internist and public health specialist Charles Daschbach, M.D., AMA Alternate Delegate; Glendale pediatrician Jess Boyer, M.D., and Phoenix internist Paul Stander, M.D., ArMA Delegates; and Sun City internist Zachary Gerbarg, M.D., and Yuma radiologist L. Keith Madison, M.D., ArMA Alternate Delegates. ■

New Active Members

The Arizona Medical Association welcomes the following new members:

COCONINO

Michael I. Vengrow, M.D.
Neurology
710 North Beaver Street
Flagstaff
University of Massachusetts
Medical School - 1977

MARICOPA

Cary B. Feinglass, M.D.
Cardiovascular Diseases
10250 North 92nd Street
Suite 300, Scottsdale
Loyola University of Chicago
School of Medicine - 1981

Alan R. Snyder, M.D.
Anesthesiology, Obstetrics
& Gyenecology
219 E. Virginia, Phoenix
Northwestern University
Medical School - 1980

Gordon J. Young, M.D.
Family Practice
1835 West Missouri Avenue,
Phoenix
University of Colorado
School of Medicine - 1974

PIMA

John E. Easa, M.D.
Anesthesiology
3390 North Campbell Avenue,
Suite 110, Tucson
Medical College of
Ohio at Toledo - 1983

Paul F. Gregory, M.D.
Internal Medicine
1980 West Hospital Drive
Suite 304, Tucson
Rush Medical College
Chicago - 1981

Paul R. Horwitz, M.D.
Ophthalmology
1980 West Hospital Drive,
Suite 311, Tucson
Rush Medical College
Chicago - 1981

Tyler J. Kent, M.D.
General Surgery
310 North Wilmot Road
Suite 102, Tucson
University of Arizona
College of Medicine - 1973

Stanley S. Racz, M.D.
Internal Medicine
P.O. Box 1227, Green Valley
Ohio State University
College of Medicine - 1977

NEW ASSOCIATE MEMBER

PIMA

Shirley L. Rivers, M.D.
Internal Medicine, Hematology,
Blood Banking
222 South Cherry Avenue, Tucson
Bowman Gray School of Medicine
Wake Forest University - 1950

NEW RESIDENT MEMBERS

MARICOPA

Nancy A. Croker, M.D.
Family Practice
Good Samaritan Medical Center
Indian University
School of Medicine - 1985

David W. Gannon, M.D.
Family Practice
St. Joseph's Hospital & Medical
Center
University of Arizona
College of Medicine - 1984

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Physicians in the News

John J. Kelley, M.D.

The Maricopa County Bar Association has honored Maricopa County Medical Society president **John J. Kelley, M.D.**, with its annual Liberty Bell award. The award is presented to the community member deemed to have made the most outstanding contributions to the American system of freedom under law.

Dr. Kelley, a neurosurgeon who trained at the Mayo Clinic, has served on the bar association's Merit Selection Commission for almost a dozen years. The commission, which meets for more than a full day four times a year, interviews and screens candidates for appointment to the Arizona Superior Court. Dr. Kelley was among the first commission members appointed by Governor Raul Castro after the commission was established in 1975. All commission members are volunteers who are not reimbursed for their time.

Dr. Kelley was cited for his dedication and commitment to the quality of the judiciary. He was selected from nominations submitted by more than 200 organizations asked to submit candidates whose activities have:

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Scottsdale allergy specialist **Merle S. Scherr, M.D.**, recently returned from East Africa, where he spent three weeks teaching and working with the medical staff at the Aga Khan Hospital and Medical Center in Nairobi, Kenya.

"There are no Board certified allergists in Kenya," Dr. Scherr explained, "so almost all of the general practice physicians treat allergy problems as part of their practice. Also, their medicines are different from American pharmaceuticals."

Dr. Scherr, who was Board certified in 1975, gave a one-day formal seminar on asthma and allergies, presenting information about diagnosis and treatment with both African and American medicines. He then spent almost three weeks working informally with the hospital medical staff in one-on-one meetings.

Merle S. Scherr, M.D.

"The allergy problems are basically the same as ours," he said. "They have the same diseases and symptoms. They do lack some of the technology and lab techniques that we have available to us here and their drug use is different. It was a matter of introducing them to our knowledge about diagnosis and managing clinical conditions with their medicines and with our American medicines."

Editor's Message

(Continued from page 1)

sonal and satisfying relationship ("He really *cares* for me!"). In contrast, the search tends to be more impersonal and more technical for the patient, and is fraught with much apprehension and occasionally scepticism ("we'll wait for the x-ray report" or "the lab results aren't back yet!"). My mother's response then was not inappropriate but reflected this process. We need to place more importance on this aspect of patient care in our everyday activities. ■

Marshall B. Block, M.D., Editor

Dementia May Be First Sign of AIDS Infection

Scientists from Memorial Sloan-Kettering Cancer Center in New York City have reported evidence that a form of dementia may be the first or only early clinical manifestation of the human immunodeficiency virus (HIV)—the causative agent in AIDS—when some victims are first seen by a physician.

The findings were detailed in a scientific article, "The Acquired Immunodeficiency Syndrome Dementia Complex as the Presenting or Sole Manifestation of Human Immunodeficiency Virus Infection," by authors Bradford A. Navia, M.D., and Richard W. Price, M.D., Department of Neurology, Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, N.Y., published in the *Archives of Neurology*, 44, January 1987, pp. 65-69.

Physicians treating AIDS patients have recognized and described a progressive dementia often accompanied by changes in personality and difficulty in movement. These phenomena have been termed the AIDS dementia complex and are characterized predominantly by cognitive impairment, failure of muscular coordination, and personality change. Approximately 25 percent of the AIDS patients seen at Sloan-Kettering initially had neurological symptoms suggestive of the AIDS dementia complex with only a mild array of other physical symptoms related to AIDS. The authors contend that the AIDS dementia complex should be incorporated into the diagnostic definition of AIDS.

In reviewing the medical records of 112 patients with the AIDS dementia complex, the researchers identified 29 cases in which this syndrome developed before a formal diagnosis of AIDS was established. Presence of HIV infection was confirmed in this group by the ultimate development of full-blown lethal AIDS or at autopsy. The earliest signs of the dementia are mental slowing with impaired memory and concentration. Most of those with AIDS dementia complex deteriorated within months to severe dementia, which left them bedridden, incontinent and unable to speak.

In most AIDS cases, neurological symptoms develop some time after the onset of ther AIDS-related changes. And despite the increasing number of AIDS patients diagnosed each year, AIDS dementia complex often goes unrecognized. Yet in perhaps as many as 25 percent of cases, AIDS dementia complex may be the sole diagnostic indicator for the illness before other symptoms are apparent. The syndrome has been further identified on the basis of atrophy of certain brain regions evidenced by CT scanning, magnetic resonance imaging and electroencephalographic recording.

One possible explanation for the early onset of neurological symptoms, according to the authors, is that the brain harbors HIV soon after the virus is introduced into the host. Thus, AIDS dementia complex may be the earliest—or even the only—marker for the clinical recognition of AIDS in some victims.

Radioactive Implant Helps Fight Cancer

Numerous studies indicate lumpectomy plus radiation therapy produces the same survival rate as modified radical mastectomy in patients with early breast cancer, and suggest local recurrence rates may be lower in patients who undergo radiation.

Now, a study in June's *Archives of Surgery* concludes that immediately implanting a tiny radioactive source at the tumor site after lumpectomy may reduce local failure rates even further.

William R. Jewell, M.D., of the University of Kansas Medical Center, Kansas City, and colleagues used the technique to treat 110 breast cancers in 107 patients over a more than four-year period.

The women underwent simple tumor excision, immediate implantation with irridium 192, and complete axillary node dissection followed by external beam radiation therapy. There were two recurrences over the follow-up period, the study says.

"These preliminary data suggest that local treatment failure can be minimized by aggressive, immediate intraoperative implantation of the tumor bed with irridium 192," it concludes.

Leukemia Support Group Provides Help

A support group for leukemia patients, their family members and friends is successfully moving into its second year of helping people cope with leukemia and related diseases, according to the Arizona Chapter of the Leukemia Society of America.

The group meets at 7:00 p.m. on the first and third Thursdays of each month under the direction of oncology counselor/facilitator Barbara Haber, M.A.

Physicians who want to refer patients to the support group are asked to call Ginny Furrer, patient aid coordinator at the Leukemia Society, 256-7693, or Barbara Haber at Good Samaritan Hospital & Medical Center, 239-2000, Beeper, #8341.

ASU Renames Center for Health Services Administration

The Center for Health Services Administration in the Arizona State University College of Business recently was renamed the School of Health Administration and Policy, following approval by the Arizona Board of Regents. "The name change reflects an expanded commitment to graduate education, community involvement and research," said Eugene S. Schneller, Director.

The School is planning a major recruiting effort to expand the size of its Master in Health Services Administration degree program, which prepares students for careers as administrators of hospitals and health care organizations, consultants to health management firms and accounting firms and policy makers in state and federal government agencies. Approximately 18 of the program's 180 alumni in major management positions throughout the United States will participate in the recruiting project.

The School's commitment to the health care community is reflected in the faculty's involvement with various state and national organizations that address problems related to the cost of health care, medical indigency and access to care.

The increased research efforts of the School's faculty will focus on the organization, quality and financing of health services in Arizona and the United States and on the major innovations in health services delivery in the United States and abroad. Faculty in the School of Health Administration and Policy have received research funding from the U.S. Department of Health and Human Services, the Robert Wood Johnson Foundation, the Flinn Foundation, the Commonwealth Fund and a variety of industry sources.

The School is accredited by the Accrediting Commission on Education for Health Services Administration. It is the only accredited graduate program in health services administration in the state and one of seven such programs in the western United States.

A member of the Association of University Programs in Health Administration and the Western Network for Education in Health Services Administration, the School cooperates with the Western Network in offering the Executive Master's in Health Services Administration at the University of Colorado in Denver and the Western Network Institute for Healthcare Executives at the University of California at Berkeley.

Over $350,000 Pledged To Children's Hospital

Arizona residents pledged more than $350,000 during the two-day Children's Miracle Network Telethon in late June, an 11 percent increase over the amount raised in 1986.

The funds will be used to assist Phoenix Children's Hospital in providing care to children with special medical needs, according to Phoenix Children's Hospital Community Relations Manager Amy Petrovsky.

She extended the hospital's gratitude for all the support provided by members of the Arizona Medical Association which helped make "miracles happen" for the children in the Arizona community.

Eyes Threatened By Gravity Inversion

Gravity inversion — hanging upside down by the legs or ankles — is advocated by some for exercise and to ease back pain. But this practice sharply increases intraocular pressure and can produce temporary vision problems, according to a report in June's *Archives of Ophthalmology*.

George E. Sanborn, M.D., of the University of Texas Health Science Center, Dallas, and colleagues tested vision in 10 normal subjects during gravity inversion. Average intraocular pressure more than doubled while hanging upside down, the study says, and transient, reversible visual field defects were detected in 11 of 19 eyes examined. Although it is unclear whether repeated inversion could harm vision permanently, the researchers recommend

an ophthalmologic examination prior to "habitual recreational or therapeutic use of inversion equipment."

People with a family history of glaucoma or abnormal vision exam results "probably should be discouraged from using inversion altogether," they say.

Laser Surgery for Skin

Laser surgery for skin problems has acceptable risks, but complications are not uncommon, a study in the March *Archives of Dermatology* reports. Suzanne M. Olbricht, M.D., of Beth Israel Hospital and Harvard Medical School, Boston, surveyed 139 dermatologists and plastic surgeons about their experience with complications in cutaneous laser surgery. Reported complication rates varied from 0 to 35 percent; means ranged from 2.8 percent to 6.2 percent, depending on th type of laser used. The mose oftennoted complication was hypertrophic scarring; others included infection, pain and hemorrhage. No procedure-related eye damage or deaths were noted. "Complications from the use of the argon and carbon dioxide lasers are currently far from rare," the study concludes, "and it is essential that both practitioners and patients fully understand the risks associated with these procedures."

Daycare Injuries Worthy of Note

Injuries to children in daycare centers appear to be a common problem deserving greater attention from pediatricians and parents, a study in the March *American Journal of Diseases of Children (AJDC)* concludes. Petra Froehlich Landman, M.D., M.P.H., of Sinai Hospital, Baltimore, and Gary B. Landman, M.D. Ph.D, of the Johns Hopkins Hospital, Baltimore, surveyed licensed group day-care centers serving 2-to-6-year-old children in Maryland and calculated a total yearly injury rate of 11.3 percent at centers responding. This was similar to incidence figures for injuries to children in the general population, the study says. Despite limits in the data, "it cannot be assumed that a regulated, licensed day-care center is as safe an environment as it could be," the authors say. "Physicians and parents must become active participants in the selection and maintenance of quality day-care programs."

Interferon Treatment for Multiple Sclerosis

Natural human fibroblast interferon (interferon beta), administered intrathecally (injected into the spinal canal), is effective at easing multiple sclerosis (MS) flare-ups, concludes a two-year, multi-center study reported in June's *Archives of Neurology*. Lawrence Jacobs, M.D., of the State University of New York School of Medicine, Buffalo, and colleagues say the randomized, double-blind study found the mean reduction in exacerbation rates for 34 MS patients receiving a placebo. In 95 percent of the recipients, "interferon beta therapy was well-tolerated, and the side effects were clearly acceptable for the benefits achieved," the study says. The results confirm those of an earlier preliminary study, say the researchers, but they cannot explain the mechanism by which the interferon seems to work.

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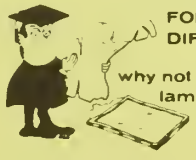

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Peripheral Blood and Bone Marrow Abnormalities in the Acquired Immunodeficiency Syndrome

MICHAEL FRONTIERA, MD, *and* ADAM M. MYERS, MD, *Denver*

In reviewing the peripheral hematologic manifestations, bone marrow changes and clinical course in 41 consecutive patients with acquired immunodeficiency syndrome (AIDS), frequent findings included anemia (95%), leukopenia (76%), bone marrow hypercellularity (73%) and pancytopenia (41%). These hematologic abnormalities were not clearly associated with specific clinical manifestations of AIDS, but support the conclusion that the hematopoietic system is a target organ in AIDS. The mechanisms of these abnormalities still need to be evaluated. Clinicians should be aware of these commonly encountered changes.

(Frontiera M, Myers AM: Peripheral blood and bone marrow abnormalities in the acquired immunodeficiency syndrome. West J Med 1987 Aug; 147:157-160)

Hematologic abnormalities are often encountered in patients with the acquired immunodeficiency syndrome (AIDS). The abnormalities vary but peripheral cytopenias are most commonly seen.[1-7] Myelodysplastic features have also been described[8] and correlations drawn between marrow cellularity and peripheral cytopenia.[9] We report a high incidence of peripheral cytopenia often with associated striking bone marrow hyperplasia. The bone marrow and peripheral blood findings of 41 patients with AIDS are described. Clinical characteristics of the patient population are reviewed and presented with the hematologic changes.

Patients and Methods

The medical records of 64 consecutively confirmed cases of AIDS at the University of Colorado Health Sciences Center and affiliated hospitals were reviewed. All the patients met the Centers for Disease Control criteria for the diagnosis of AIDS.[10] Most of these patients had been seen by one of us in a clinical setting. The diagnosis of AIDS was made in this cohort during a 39-month period from May 1982 through August 1985, with most of the cases being seen during the latter part of this time span.

Of the 64 patients, 41 had bone marrow examinations, which form the basis of this review. Clinical characteristics and course were determined by chart review. Bone marrow aspirations with biopsies and peripheral complete blood counts were done concurrently. After informed consent, bone marrow cores were taken from the posterior iliac crest using a Jamshidi needle. Specimens were first placed in B5 fixative for two hours and then in 10% buffered formalin until processed. The cores were decalcified in 1.35N hydrochloric acid for one hour and embedded in paraffin. Thin sections were stained with commercially available Wright's, Giemsa's, Silver methenamine, hematoxylin and eosin, Ziehl-Neelsen and Prussian blue. Reticular stains were not routinely done. Bone marrow cellularity was determined by two observers.

At the time of the bone marrow examination, all the patients had or were thought to have the diagnosis of AIDS. Most bone marrow examinations were done to investigate peripheral hematologic abnormalities, but five were done at autopsy. Other indications prompting bone marrow study were fever of unknown origin, culture for disseminated infectious diseases or staging for lymphoma. Circulating T-lymphocyte subsets were quantitated using commercially available monoclonal antibody (OK T4 for T-helper/inducer cells and OK T8 for T-suppressor/cytotoxic cells).

Results

All patients in the study group were men ranging in age from 23 to 62 years, with a median age of 39 years. All were admittedly homosexual except three. One of the three had hemophilia and had received factor VIII concentrate for longer than 10 years, the second patient had intraoperative blood transfusions three years previously and the third patient was a heterosexual man who had contacts with prostitutes. This last patient presented with a rapidly fatal illness and at autopsy was found to have disseminated *Pneumocystis carinii* pneumonia and cytomegalovirus infection. Of the 41 patients, 12 admitted to recreational intravenous drug use. *P carinii* pneumonia was documented in 27 patients, 14 of whom were treated with trimethoprim and sulfamethoxazole (TMP/SMX). In all, 25 patients had other opportunistic infections, either alone (6 patients) or in combination with *P carinii* pneumonia (19 patients).

All of the 41 patients have died of their disease. The median survival after the diagnosis of AIDS was 7.6 months. The causes of death were often combinations of advanced Kaposi's sarcoma, opportunistic infections and extreme inanition associated with advanced infection with the human immunodeficiency virus.

T-cell subset evaluations were completed in 35 patients. The OK T4-OK T8 ratios were less than 1.0 in 33 (94%) and less than 0.4 in 22 (63%) patients. This aberration in the ratio

From the Department of Medicine, Division of Hematology (Drs Frontiera and Myers), University of Colorado Health Sciences Center, and the Division of Hematology-Oncology (Dr Myers), Denver General Hospital, Denver.

Reprint requests to Adam M. Myers, MD, Division of Hematology, Denver General Hospital, 777 Bannock St, Denver, CO 80204-4507.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
TMP/SMX = trimethoprim/sulfamethoxazole

TABLE 1.—*Bone Marrow Cellularity Versus Peripheral Abnormalities**

Cellularity, %	Patients, number	Leukopenia and Anemia	Thrombocytopenia and Anemia	Pancytopenia
<25	2	2	2	2
>25 <50	13	7	7	5
≥50	26	20	15	10

*Leukopenia is defined as a leukocyte count of <4,000 per μl; thrombocytopenia is defined as a platelet count of <150,000 per μl, and anemia is defined as a hematocrit of <40%.

of helper cells to suppressor cells was due to a pronounced reduction in the number of helper cells and a significant increase in the number of suppressor cells, which is consistent with the diagnosis of AIDS.

Peripheral cytopenias were not directly predictive of the subsequent cellularities found on marrow biopsy. Cytopenic patients were more likely to have hypercellular marrows (Table 1). Of the 41 patients, 26 (63%) had marrow cellularities of 50% or more. Of these 26 patients, 10 had pancytopenia. Thirteen patients (32%) had normal cellularity defined as being greater than 25% and less than 50%; of these, 5 had pancytopenia. Only two patients had hypocellular marrows and both had pancytopenia. One of these patients had hemophilia and the other was a patient with advanced Kaposi's sarcoma treated with vinblastine sulfate.

The clinical manifestations of AIDS and its correlations with the peripheral hematologic abnormalities are presented in Table 2. Of the 27 patients with *P carinii* pneumonia, 14 had been treated with TMP/SMX before marrow biopsy. Most of these patients had significant peripheral cytopenias and yet had marrow hypercellularity. This was also seen in the patients with *P carinii* infection who had not received TMP/SMX at the time of biopsy. In fact, peripheral cytopenia associated with marrow hypercellularity was commonly observed also in patients with opportunistic infections other than *P carinii* pneumonia, Kaposi's sarcoma alone and lymphoma. This striking tendency toward peripheral cytopenia, often with marrow hypercellularity, occurred independent of the clinical manifestations of AIDS or exposure to TMP/SMX.

The patients' therapy included the use of a variety of other medications within one month of bone marrow examination. Fourteen patients had received various antibiotic combinations for treatment of disseminated *Mycobacterium avium-intracellulare* infection, *Mycobacterium tuberculosis* or other nontuberculous infections. Six patients had received ketoconazole for fungal disease. Five patients had received cytotoxic chemotherapy for Kaposi's sarcoma. Two patients were given vinblastine, two patients were treated with a combination of vincristine sulfate and methotrexate and one was given doxorubicin (Adriamycin) hydrochloride and bleomycin sulfate. One of the patients who had received vinblastine died two weeks after receiving the chemotherapy. This patient was one of the two patients with a hypocellular bone marrow and accompanying pancytopenia. In this case, the hematologic changes may have been associated with therapy. The other patients who received chemotherapy did not show any clear bone marrow effect to account for peripheral hematologic abnormalities. Leukopenia occurred in 79% of the patients treated with trimethoprim and sulfamethoxazole, while 67% of the remaining 27 patients had leukopenia. If the five patients who received cytotoxic chemotherapy are excluded from consideration, the incidence of leukopenia becomes 92% in TMP/SMX-treated patients while 75% of the remaining 24 patients had leukopenia. No clear cause and effect between TMP/SMX use can thus be established to explain the leukopenia, although there is a trend suggesting a higher proportion of neutropenic patients among those receiving TMP/SMX.

Splenomegaly was documented clinically in eight patients. There was no correlation between thrombocytopenia and bone marrow megakaryocyte numbers seen in these patients. Lymphoma was identified in two patients. On histologic examination, both lymphomas were of high grade with an abdominal origin in one patient and a central nervous system origin in the other.

Peripheral hematologic abnormalities were extremely common. Anemia was the most common abnormality seen, with hematocrits of less than 40% seen in 39 of the 41 patients (95%). The average hemoglobin was 9.8 grams per dl. Reticulocyte counts, even in those patients with severe anemia, were greatly depressed. Moderately severe anemia with hematocrits less than 30% was noted in 56% of the patients.

Leukopenia, defined as a total leukocyte count of less than 4,000 per μl, was present in 76% of the patients. Only 12% of the patients had a leukocyte count of greater than 7,000 per μl. The peripheral leukocyte differentials commonly showed a leftward shift, with a moderate number of immature neutrophils present. A relative lymphopenia along with increased monocyte numbers was typically seen on the peripheral smears. Table 3 shows the absolute counts obtained in the ten patients with pancytopenia and concomitant bone marrow hy-

TABLE 2.—*Clinical Manifestations of AIDS Correlated With Hematologic Abnormalities**

Patient Group	Patients, number	Leukopenia and Anemia	Thrombocytopenia and Anemia	Pancytopenia	Increased Marrow Cellularity
Pneumocystis carinii pneumonia with TMP/SMX treatment	14	11	6	5	10
Pneumocystis carinii pneumonia without TMP/SMX treatment	13	7	10	5	8
Other opportunistic infections	6	5	2	2	5
Kaposi's sarcoma	6	5	6	5	5
Lymphoma	2	1	0	0	2

AIDS=acquired immunodeficiency syndrome, TMP/SMX = trimethoprim/sulfamethoxazole

*Leukopenia is defined as leukocyte count of <4,000 per μl; thrombocytopenia is defined as a platelet count of <150,000 per μl, and anemia is defined as a hematocrit of <40%

percellularity. These differentials and clinical characteristics were similar to those seen in the entire group.

Thrombocytopenia was also common: 59% of the patients had platelet counts of less than 150,000 per μl. The range of thrombocytopenia seen in these patients was great. Only 12% of the patients had a platelet count greater than 250,000 per μl. None of the patients with normal or hypercellular marrow showed a decreased number of megakaryocytes.

Pancytopenia was present in 17 of the 41 patients studied. The clinical data of the ten pancytopenic patients with bone marrow hypercellularity are presented in Table 3. The clinical manifestations of AIDS, time since diagnosis (not shown in table) and treatment given were compared to the hematologic changes, and no clear correlations were found. The percentages of lymphocytes and plasma cells seen in these representative bone marrows are also shown.

The bone marrow biopsy of patient 1, shown in Figure 1, was representative of the hypercellularity and lymphocytic infiltrations seen. Although lymphocytic and plasmacytic marrow infiltration was prominent, the hypercellularity was accounted for primarily by a striking trilinear hyperplasia. There were no abnormalities in maturation noted in either erythroid or myeloid lines. In general, there was an elevated myeloid to erythroid ratio. Some marrow specimens also had areas of focal necrosis and serous fat atrophy.

Discussion

The incidence of AIDS is increasing rapidly worldwide. In the United States 13,000 cases were reported in 1986.[11] AIDS is a systemic disease with multiple complications. This report further confirms the hematopoietic system as another target organ in AIDS. The clinical and laboratory characteristics of our patients were typical of patients with AIDS. The most striking observation in our patients was the degree of marrow hyperplasia encountered, often with concomitant peripheral pancytopenia (Tables 1 and 2). Of 64 patients, 39 had anemia. The degree of anemia did not correlate with any clinical manifestation of AIDS. The reticulocyte counts were depressed, with only one patient having a mild elevation of the reticulocyte count in the face of anemia. The rest evidenced no peripheral responsiveness to their anemia while concurrent bone marrow studies commonly showed erythroid hyperplasia at all stages of maturation and increased iron stores. These changes suggest ineffective erythropoiesis, but

TABLE 3.—*Patients With Pancytopenia and Bone Marrow Hypercellularity*

Patient	*Age, yr*	*Clinical Status*	*Marrow Cellularity, %*	*Myeloid: Erythroid Ratio*	*Lymphocytes and Plasma Cells, %*	*Total Neutrophils, /μl*	*Total Lymphocytes, /μl*	*Hct, %*	*Platelets**	*T-cell Helper-Suppressor Ratio*	*Iron Concentration*	*Medication Within 30 d*
1 . . .	32	KS	90	1:2	<10	1,925	1,400	31.2	110	0.67	↑	Triazolam
2 . . .	36	KS	90	3:1	18	2,457	1,092	32.4	141	0.29	N	Phenytoin
3 . . .	36	PCP, Crypto	85	3:1	<10	790	190	18.0	64	0.60	N	TMP/SMX
4 . . .	28	KS	80	1:2	15	720	800	27.5	94	0.08	↑	Vitamins
5 . . .	44	KS, MAI and CMV infection	70	7:1	<10	1,634	38	19.7	42	. . .	↑	TMP/SMX
6 . . .	36	KS, PCP	65	10:1	10	1,360	255	31.8	120	0.39	N	TMP/SMX
7 . . .	53	PCP	60	3:1	<10	1,584	90	33.0	140	0.08	↑	Cefazolin
8 . . .	45	PCP	50	2:1	<10	1,586	832	30.7	125	0.04	↑	TMP/SMX
9 . . .	31	KS, PCP, MAI infection	50	4:1	20	2,100	150	36.1	86	0.20	↑	None
10 . . .	28	KS	50	3:1	10	3,120	780	24.9	23	0.75	↑	TMP/SMX

CMV=cytomegalovirus, Crypto=cryptococcosis, Hct=hematocrit, KS=Kaposi's sacroma, MAI=*Mycobacterium avium-intracellulare*, N=normal, PCP=*Pneumocystis carinii* pneumonia, TMP/SMX=trimethoprim/sulfamethoxazole, ↑=increased

* $\times 10^3$ per μl.

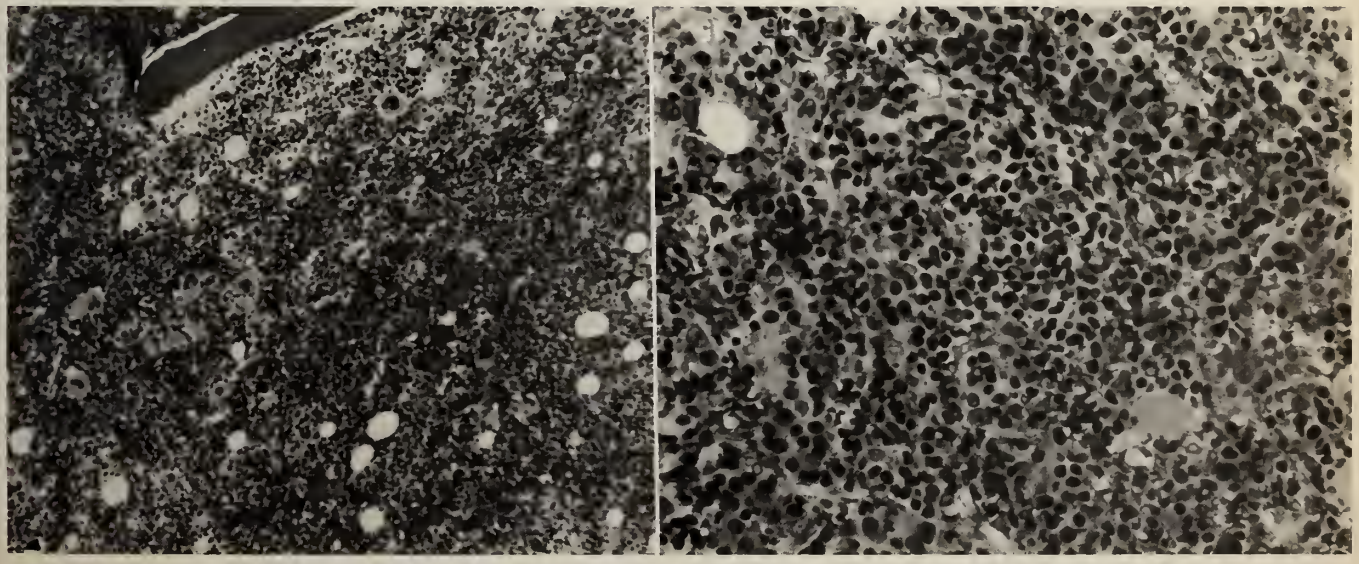

Figure 1.—Bone marrow biopsy from patient 1. **Left,** Light microscopy shows trilinear hyperplasia and hypercellularity (hematoxylin and eosin, original magnification × 100). **Right,** A higher magnification shows an increased number of lymphocytes and plasma cells (hematoxylin and eosin, original magnification × 400).

no mechanism of action was apparent, although the findings were most consistent with anemia of chronic disease. Infection, Kaposi's sarcoma or constitutional abnormalities associated with this ill patient population could be contributing factors. Another possible explanation for the anemia could be the potentially marrow-toxic drugs administered to some of the patients. Bone marrow hypercellularity and peripheral cytopenia occurred to an equal degree regardless of medication received in treatment. Marrow erythrophagocytosis, which has been reported by other observers,[1] was not seen in our patients. Alternatively, one could speculate about abnormal release mechanisms, changes in cell-cell interactions or autoimmune inhibition to explain the ineffective hematopoiesis.

Peripheral leukopenia, in addition to the usual lymphopenia, was also seen associated with bone marrow granulocytic hyperplasia at all stages of maturation. This finding suggests either increased turnover with accelerated peripheral utilization or ineffective granulopoiesis. There were no maturational abnormalities seen. Specifically, there were no megaloblastic features, as might have been encountered, since the use of trimethoprim/sulfamethoxazole has been associated with these findings. In addition, while the use of TMP/SMX has been associated with a striking tendency to neutropenia in AIDS patients,[12] patients in our study consistently had neutropenia, even when not receiving a sulfa-based compound.

Thrombocytopenia was also commonly encountered, as has been described in AIDS patients.[13] All bone marrow specimens reviewed showed normal or increased megakaryocyte numbers suggesting either ineffective thrombopoiesis or increased peripheral destruction as opposed to a hypoproliferative process. There are data reported by others consistent with an immune-mediated mechanism involving the deposition of immune complexes on platelet surfaces.[14] Assays were done on two of our thrombocytopenic patients (platelet count $< 50{,}000$ per μl) and showed an immunoglobulin antiplatelet antibody present, which is a nonspecific finding. Splenomegaly was present in eight patients and, in these cases, platelet sequestration may have contributed to the thrombocytopenia.

Lymphoid aggregates or an increased number of lymphocytes distributed throughout the marrow population of cells was seen in most of our patients. An increased number of plasma cells was also noted. This is a common finding in the marrows of AIDS patients as described by others.[1-9]

In summary, the often striking marrow hyperplasia with concomitant peripheral cytopenia identifies the bone marrow as another frequently targeted organ system in the acquired immunodeficiency syndrome. The disparity between peripheral cytopenia and marrow hyperplasia suggests mechanisms of either ineffective hematopoiesis, abnormal release or increased peripheral destruction. The clinical situation in patients with AIDS is often complex, and the cause of the hematologic abnormalities encountered may also be associated with infections, malignancy and drug treatments. It is quite possible, however, that these abnormalities are primary to the immune disturbance that characterizes this syndrome as suggested in part by the presence of increased numbers of marrow lymphocytes and plasma cells seen in the bone marrow. These mechanisms need to be further evaluated.

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Diagnostic Value of Thyrotropin-Releasing-Hormone Stimulation in Patients With Pituitary Tumor

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Plasma prolactin response to thyrotropin-releasing-hormone (TRH) stimulation was diminished in 30 patients with prolactinomas and 9 patients with acromegaly who had normal serum prolactin levels. There was no overlap of prolactin responses when compared with 32 control patients. Responses of ten patients with adrenocorticotropin (ACTH)-secreting pituitary tumors were similar to those of controls. Plasma growth hormone concentrations after TRH stimulation changed significantly in 28% of normal control and 20%, 25% and 50% of patients with prolactin-, growth hormone- and ACTH-secreting pituitary tumors, respectively. Our data suggest that the blunted TRH-induced rise in plasma prolactin levels in patients with prolactinomas and those with acromegaly may be related to humoral factor(s) affecting TRH receptor or postreceptor function. Growth hormone responses to TRH are nonspecific and should not be considered a marker for active acromegaly.

(Cook DM, Greer MA, Paxton H: Diagnostic value of thyrotropin-releasing-hormone stimulation in patients with pituitary tumor. West J Med 1987 Aug; 147:161-164)

The exact mechanism(s) responsible for the blunted plasma prolactin responses to thyrotropin-releasing-hormone (TRH) stimulation in patients with prolactinomas is unknown. TRH receptors have been found on human prolactinoma cells.[1] In vitro responses of these cells to TRH administration have been variable.[2,3] In most patients with hyperprolactinemia not caused by a pituitary tumor, there is a normal prolactin secretory response to TRH,[4-8] suggesting that ultrashort-loop feedback of prolactin on lactotrope activity is not responsible for the decreased response in prolactinoma patients.

We wondered if the presence of any hypersecreting pituitary tumor might blunt responses to TRH. A tumor mass might impair the local blood supply and thus the delivery of TRH to prolactin-secreting cells, accounting for inadequate responses. Patients with prolactinomas were compared with patients with adrenocorticotropin (ACTH)- and growth hormone-secreting tumors. We found the responses of patients with acromegaly were similar to those of patients with prolactinomas, and patients with ACTH-secreting tumors had responses similar to those of controls. Our studies suggest humoral and not mass lesion effects may explain blunted responses and that growth hormone- and prolactin-secreting tumors are capable of inhibiting prolactin responses to TRH, possibly by a similar mechanism.

Patients and Methods

Controls

Six men and 26 women were studied initially because abnormal pituitary function was questioned clinically. Typical problems included mild obesity (possible Cushing's disease), coarse facial features (possible acromegaly) and possibly a partially eroded sella (verified later as normal by computed tomographic [CT] scan). All findings later proved to be normal except in two patients with primary hypothyroidism and one with drug-induced (thioridazine hydrochloride [Mellaril]) hyperprolactinemia. The two patients with hypothyroidism had pituitary enlargement and hyperprolactinemia: pituitary size and prolactin concentrations reverted to normal with thyroxine therapy.

Prolactinoma

In all, 23 women and 7 men had prolactinomas verified by a surgical procedure. All patients had elevated basal plasma prolactin concentrations. Plasma growth hormone concentrations were normal and suppressed with glucose. All were studied during the preoperative period.

Acromegaly

Four men and five women had acromegaly associated with elevated growth hormone concentrations not suppressible by glucose. None had hyperprolactinemia. All were studied preoperatively.

Cushing's Disease

Ten patients with ACTH-secreting pituitary tumors had detectable levels of plasma ACTH. The diagnosis was established by standard dexamethasone suppression and metyrapone stimulation tests. Plasma growth hormone concentrations were suppressed by glucose in all patients to undetectable levels. All tumors were verified by a pituitary operation. All patients except one were cured by surgical therapy.

All patients were admitted to the Clinical Research Center of the University of Oregon Health Sciences Center. Testing was done between 8 AM and 9 AM in the fasting basal state. After informed consent, 500 μg TRH was given as an intrave-

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ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropin
CT = computed tomography
RIA = radioimmunoassay
TRH = thyrotropin-releasing hormone

nous bolus via an indwelling venous catheter. A blood specimen was taken at 0, 20 and 40 minutes through the same catheter and assayed for prolactin and growth hormone by described techniques. Growth hormone was assayed by double-antibody radioimmunoassay (RIA) (BIO-RIA Incorporated, Montreal, Canada). Prolactin was assayed by double-antibody RIA (Diagnostic Products Corporation, Los Angeles).

Results

Prolactin responses to 500 μg TRH are shown in Figure 1. Peak responses were predominantly at 20 minutes, but those occurring at 40 minutes are not identified separately.

Peak plasma prolactin responses are expressed as a percentage increase from basal. TRH-induced changes in plasma prolactin concentrations were significantly different when patients with prolactinomas were compared with either controls ($P < .00001$) or patients with ACTH-secreting tumors ($P < .00001$; Kruskel-Wallis analysis of variance). Patients with growth hormone-secreting tumors had significantly different responses from those of controls ($P < .00001$). There was no significant difference in responses between patients with prolactinoma and those with acromegaly ($P < .5$). Responses expressed in nanograms per milliliter are shown in Figure 2 for all patients studied.

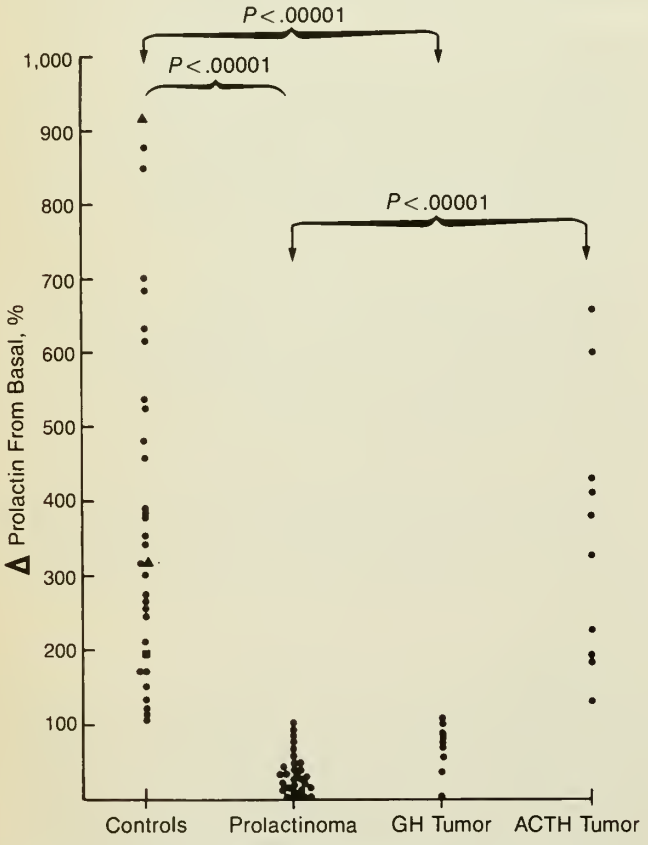

Figure 1.—The percent change in plasma prolactin levels in response to the administration of 500 μg of thyrotropin-releasing hormone preoperatively is shown. Basal prolactin concentrations in the prolactinoma group ranged from 22 to 1,560 ng per ml. Two patients in the control group with primary hypothyroidism are identified by triangles and have basal prolactin concentrations of 10 and 34 ng per ml, respectively. The basal prolactin concentration of the one patient with drug-induced hyperprolactinemia (identified by a square) was 95 ng per ml. Basal prolactin concentrations were less than 20 ng per ml in all patients with growth hormone (GH)- and adrenocorticotropin (ACTH)-secreting tumors and in the remaining control patients.

Individual basal and peak plasma growth hormone concentrations after TRH stimulation in the four groups are shown in Figure 3. A growth hormone response is defined arbitrarily as a level rising 100% or more above basal and a 5-ng-per-ml rise because spontaneous fluctuations could account for large percentage changes if basal values are low. Significant growth hormone responses to TRH stimulation in each group were as follows: control group 28%, prolactinoma group 20%, acromegalic group 25% and group with ACTH-secreting tumors 50%.

Postoperative Response

Not all patients were cured (Figure 4). The criteria for cure in patients with prolactinomas included normal prolactin

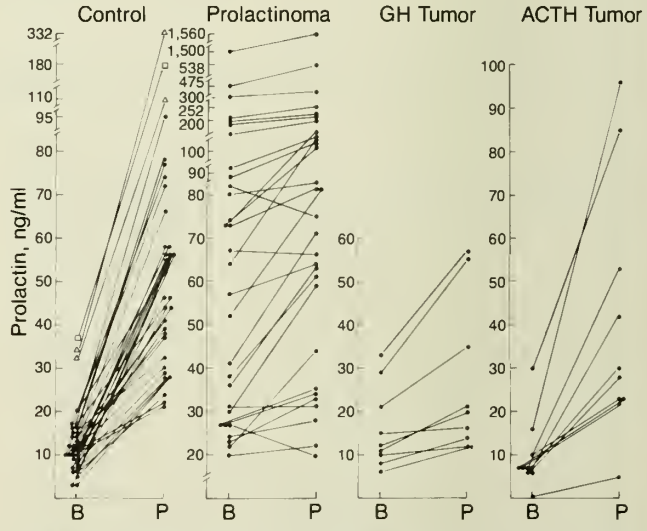

Figure 2.—The graphs show peak plasma prolactin responses (ng per ml) to thyrotropin-releasing hormone stimulation. The two patients in the control group with primary hypothyroidism are identified by triangles. The one patient with drug-induced hyperprolactinemia is identified by a square. ACTH = adrenocorticotropin, B = basal, GH = growth hormone, P = peak

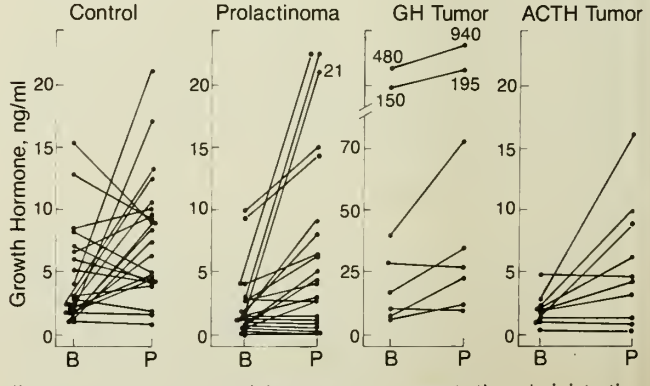

Figure 3.—Plasma growth hormone responses to the administration of 500 μg of thyrotropin-releasing hormone in a preoperative study are given. Absolute values are shown and suggest significant responses in all four groups. ACTH = adrenocorticotropin, B = basal, GH = growth hormone, P = peak

levels on at least three separate determinations and no evidence of an anterior pituitary deficiency. Patients not cured of prolactinoma included those in whom the surgeon believed not all the tumor was removed and patients who had persistent hyperprolactinemia. None of the noncured patients were thought to have hyperprolactinemia on the basis of isolation of the anterior pituitary from the hypothalamus. Prolactin responses to TRH in patients with prolactinoma and those with acromegaly were similar to those of controls in cured patients. Those not cured were persistently unresponsive. Patients with ACTH-secreting tumors were unchanged postoperatively whether cured or not. Not all patients returned for follow-up studies.

Discussion

Abnormal prolactin responses to TRH have been observed in most patients with prolactinomas.* Klijn and co-workers have suggested that this may be related to a tumor in the hypothalamic area because 7 of 11 patients they studied with suprasellar tumors that were not prolactinomas had blunted responses.[20] Our data suggest that other mechanism(s) for blunted responses may exist in growth hormone- and prolactin-secreting tumors.

It has been suggested that patients with prolactinomas may have a benign course.[21-23] Such studies that suggest spontaneous regression or stable growth characteristics, however, lack adequate proof that these patients actually have tumors. A prolactinoma may or may not be visible by high-resolution CT scan of the sella.[24-28] A reliable nonoperative means of identifying tumors would avoid an unnecessary operation and the undue worry if a tumor was not present and improve our knowledge of the natural history of this tumor. Our results suggest that prolactinoma patients do not respond to TRH stimulation with a change in plasma prolactin concentrations. Most series reporting false-positive responses do not have surgical and pathologic verification of prolactin-secreting tumors, and those that do have histologic proof tend to implicate TRH hyporesponsiveness.[7-19] Chlorpromazine stimulation tests have also been used to separate patients with prolactinomas from those with functional hyperprolactinemia. Boyd and associates found blunted prolactin responses to chlorpromazine stimulation in 4 of 6 prolactinoma patients and in 4 of 12 other patients with galactorrhea without evidence of adenoma.[15] Kleinberg and colleagues found blunted rises of serum prolactin levels after chlorpromazine stimulation in all nine patients with verified prolactinoma and in 19 of 36 patients with other forms of galactorrhea.[29] Zárate and coworkers showed normal responses to chlorpromazine in 8 of 16 patients with galactorrhea and amenorrhea, including 2 of 5 with pituitary tumors.[30] Our studies with TRH would suggest a lower incidence of false-positive responses compared with those with chlorpromazine.

Why patients with prolactinomas respond poorly to TRH stimulation is an unanswered question. Patients with hyperprolactinemia of a clearly secondary cause such as drug-induced or associated with hypothyroidism usually respond to TRH administration.[15,29,31] Other patients identified as functional may or may not respond.[7,11,12] Because this functional group has not had surgical exploration, we cannot be sure whether or not failure to respond may represent the presence of a tumor. Our series includes two patients with hyperprolactinemia due to hypothyroidism and one due to drug-related causes. All these responded vigorously to TRH stimulation. Our series of prolactinoma patients is important because all were clearly verified by a surgical procedure.

The finding of a persistent blunted response postoperatively in only the patients with prolactinoma and acromegalic patients not cured by surgical therapy suggests that the blunted response is not of hypothalamic origin or a generalized abnormality of lactotropes. It does suggest that a complete cure is possible by surgical treatment and that a return of prolactin responsiveness to TRH stimulation may be a marker for a surgical cure.

The diminished prolactin response to TRH administration in patients with prolactinoma and acromegalic patients is not explained at present. The absence of stored prolactin in tumor could be an explanation. We did not have immunocytochemistry staining to verify the presence or absence of prolactin in tumor cells. Clear responses in the secondary causes, however, suggest that some hyperprolactinemic states are not associated with exhaustion of stored prolactin. Pathologic studies using immunocytochemistry have verified the presence of stored hormone in some, but not all, prolactinomas. We do not know of a study showing a correlation between the absence of storage and blunted or absent prolactin responses to TRH. Until such studies are forthcoming, we will continue to look for the presence of a prolactinoma when serum prolactin responses to TRH stimulation are low or absent.

Hyperprolactinemic patients with chronic renal failure also have poor plasma prolactin responses to TRH.[32-35] Normal responsiveness does not return with dialysis but does with transplantation,[36] suggesting an inhibition at the pituitary level by a humoral factor other than prolactin because other functional causes of excess prolactin secretion such as

*References 7-13 (p 225), 14-19 (p 131).

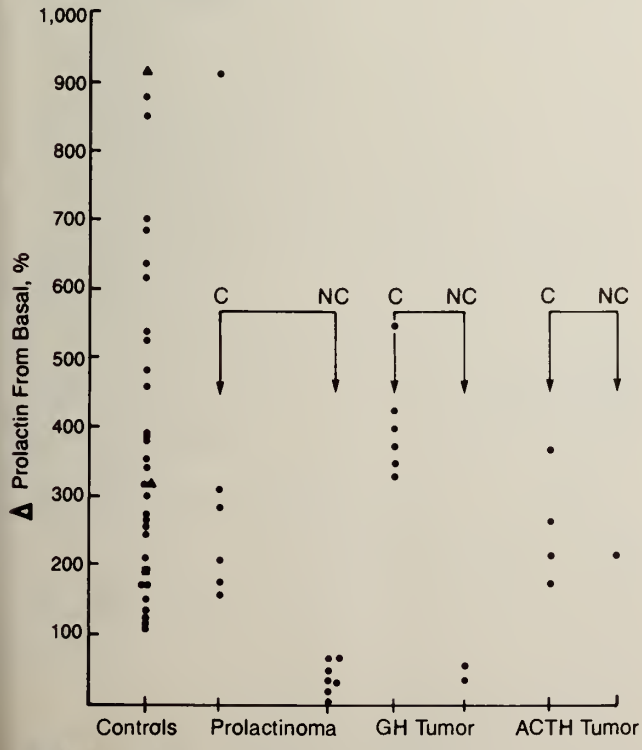

Figure 4.—Plasma responses to thyrotropin-releasing hormone stimulation reverted to normal in cured patients with prolactinomas and those with acromegaly. The responses in noncured patients in both groups were unchanged. ACTH = adrenocorticotropin, C = cured, GH = growth hormone, NC = not cured

drug-induced and primary hypothyroidism are not associated with inhibition.

The growth hormone responses to TRH observed in both control patients and those with a pituitary tumor without acromegaly were surprising. Although previous studies[35,37,38] of growth hormone responses to TRH in controls disagree with our findings, closer inspection of these reports (especially that of Irie and Tsushima[37]) suggests that growth hormone may be significantly released by TRH stimulation in control subjects. Our findings imply that growth hormone response to TRH is not an exclusive tumor marker for acromegaly as 28% of the control patients, 20% of the patients with prolactinomas and 50% of patients with ACTH-secreting tumors had significant increases in growth hormone levels. Therefore, we suggest that the current clinical practice of accepting growth hormone responses to TRH stimulation[37,39-42] as evidence for acromegaly may not be valid.

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The Sexual History-Taking and Counseling Practices of Primary Care Physicians

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As part of a statewide survey of experiences related to the acquired immunodeficiency syndrome and competencies of a random sample of primary care physicians in California done in early 1986, we interviewed 1,000 internists, family and general practitioners about their sexual history-taking and counseling practices. Less than 4% have patients complete a history form that includes questions about sexual orientation or practices, and only 10% ask new patients questions specific enough to identify those at high risk of exposure to the human immunodeficiency virus. Internists, women and younger physicians and those expressing little discomfort in dealing with gay men more often took adequate sexual histories and gave appropriate advice. Among those physicians with patients at risk of becoming infected, only half recommended the use of condoms and 60% advised a reduction in the number of partners. More than 15% recommended abstention from sexual intercourse, and 8% suggested these patients should switch to a heterosexual life-style.

(Lewis CE, Freeman HE: The sexual history-taking and counseling practices of primary care physicians. West J Med 1987 Aug; 147:165-167)

Control of the acquired immunodeficiency syndrome (AIDS) epidemic at present depends on preventing infection with the human immunodeficiency virus (HIV) through a reduction in risks of exposure.[1] Various groups are currently engaged in efforts directed at public education and the counseling of well-defined high-risk populations. Little is known, however, about the efforts of practicing physicians in the primary prevention of AIDS.

Primary care providers could play an important role in the struggle to contain AIDS. To do so, however, they must know who among their patients is at risk and how to advise them. This requires that physicians take appropriate sexual histories* and obtain data on other possible exposures through blood products and intravenous drug use. They also must know how to counsel and the relative risk of exposure to HIV in different sexual practices—that is, what constitutes "safer sex."

As part of a survey of the AIDS-related competencies of primary care physicians in California, we inquired about their sexual history-taking practices and their counseling efforts in behalf of patients at risk for AIDS. We report the findings of that survey.

Physicians and Methods

A random sample of primary care physicians (general practitioners, family practitioners and general internists) throughout California was drawn using the American Medical Association's directory file, which includes members and nonmembers. The sample was stratified by geographic region, and physicians in nonurban areas were oversampled to assure their adequate representation in the study.

A survey instrument developed in a study of Los Angeles County physicians was used with minor modifications.[2] Telephone interviews, conducted early in 1986, lasted an average of 25 minutes. About two thirds of the way through the interview, physicians were asked, "Do you have a standard medical history that new patients in your practice fill out?" (if yes) "Does this form include sexual history questions?" (if yes) "What do these questions cover?" Interviewers probed for additional responses, but did not provide specific examples of types of questions. Physicians subsequently were asked, "Do you usually ask new patients questions about their sexual history as part of the evaluation?" An affirmative response was followed by "What do these questions usually cover?" (again, repeated probes).

In an earlier section of the interview, physicians were asked if they had any patients at risk of HIV infection. Those with such patients were asked if they had counseled any of these persons about ways of decreasing their risk. If they responded in the affirmative, they were asked, "What specific things have you recommended?" Again, physicians were not offered alternatives, but interviewers probed for additional responses until none were forthcoming.

Results

Slightly more than 60% of the physicians in the sample completed an interview. There were no significant differences in the known characteristics of those who participated in the telephone survey versus those who did not. Of the respondents, 9% were women, 35% were in the practice of general internal medicine, 47% were family physicians and 18% de-

*Appropriate sexual histories, like any other area of history taking, do not involve asking the same detailed list of questions of all patients. More information is sought only as indicated by responses to previous questions.

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This study was supported in part by the Universitywide (UC) Task Force on AIDS grant No. A850612.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

scribed themselves as general practitioners. In all, 53% of respondents were in solo practice and 26% practiced in groups of four or more physicians. The median number of years in practice of those interviewed was 15 years. As indicated, physicians in the non-Standard Metropolitan Statistical Area counties in California were oversampled; they represented 31% of respondents. Almost 28% of the respondents were from Los Angeles, 20% from San Francisco and the rest (21%) were from other metropolitan areas throughout the state of California.

The telephone interviews were conducted by Marylander Marketing Associates, a firm with extensive experience in telephone surveys. Professional interviewers (N = 23) working for this firm completed a special training program before starting the survey.

About a third of the 1,000 physicians interviewed had seen and evaluated, or referred for evaluation during the previous six months, at least one patient whose symptoms were consistent with a diagnosis of the AIDS-related complex or AIDS. More than 75% of these physicians had one or more patients express concern about acquiring AIDS, and 52% indicated they had one or more patients in their practice at risk of exposure to HIV.

Table 1 summarizes sexual history-taking practices in response to the three questions posed.

The most common item on medical history forms inquired about sexual difficulties (loss of libido, failure to achieve orgasm or to maintain erections). Less than 4% of these physicians had intake forms that would identify persons at risk for AIDS by inquiring about the sex of their partners or the type of sexual practices in which they engaged.

TABLE 1.—*Sexual History-Taking Practices of 1,000 Primary Care Physicians in California*

Interview Question	*Physicians Interviewed, Percent*
Uses a questionnaire for new patients that contains sexual history items	44.5
Content of these items	
"Difficulties"	10.5
Enjoyment	6.0
Frequency of intercourse	3.5
Type of sexual practices	3.7
Sex of partners	3.4
Takes sexual history from new patient	36.2
Content of interview	
"Difficulties"	8.6
Enjoyment	6.3
Frequency of intercourse	5.6
Type of sexual practices	9.7
Sex of partners	10.0
Takes supplemental sexual history on continuing patient	38.8
Content of interview	
"Difficulties"	0.1
Enjoyment	2.4
Frequency of intercourse	2.5
Type of sexual practices	0.3
Sex of partners	0.6

A sexual history was taken from new patients by only 36% of the respondents, and 39% said they made such inquiries at the time of periodic examinations of continuing patients. The content of these inquiries most often related to difficulties with sexual function.

Table 2 illustrates the counseling practices used by physicians with patients at risk for becoming infected with HIV by region in the state.

Advice other than that listed—that is, avoiding oral sex—was offered, but these recommendations were made by less than 3% of respondents. Counseling about three rational and appropriate risk-reducing behaviors—avoiding anal intercourse, reducing the number of partners and using condoms—was not evenly distributed geographically among physicians throughout the state. Almost 1 out of 6 physicians, however, suggested sexual abstinence, and 1 in 12 advised their gay patients to switch to a heterosexual life-style.

Appropriate counseling and sexual history-taking practices were associated significantly with the age, gender and specialty of a respondent. Younger physicians do more counseling ($P < .001$) and more frequently take sexual histories (49% of those in practice less than 5 years compared with 34% of those in practice more than 30 years, $P < .005$). Women do more counseling than men (79% versus 61%, $P < .005$) and score higher in competency on sexual history taking (40% versus 33%, $P < .05$). Among the three specialties, internists do more counseling (73% versus 59% of family physicians and 50% of general practitioners, $P < .001$). The types of advice and specific questions asked did not vary by age, gender or specialty.

Physicians who said they experienced a great deal of discomfort dealing with homosexuals in their practice took sexual histories (21% versus 37%, $P < .01$) and provided adequate counseling less often (13% versus 38%, $P < .01$) than those who expressed little or no discomfort.

Discussion

The data presented are self-reported and must be interpreted in context. That is, physicians were asked about their sexual history-taking practices during an interview that focused on their experiences with and knowledge of AIDS. Certainly this should produce an inflationary effect. This, in addition to the social desirability of certain responses, should cause the data to be viewed as maximum estimations, if not exaggerations, of actual practices.

The 32% prevalence of sexual history-taking reported by physicians under circumstances similar to this—that is, in the context of a potentially sensitizing study[3]—is similar to the 36% reported in this survey.

The results suggest only a small fraction of primary care physicians in California take sexual histories from their patients. Almost two thirds of physicians indicate they did not take sexual histories on patients new to their practice. At most, only 10% of these physicians are specific enough in their history taking to obtain relevant information for assigning risks and counseling patients. The counseling practices reported leave much to be desired, as it would appear that only 60% of the physicians with patients at risk could have provided appropriate counsel useful in reducing risks.

Discomfort in dealing with gay men is a significant deter-

TABLE 2.—*Counseling Practices by Those Having Patients at Risk for AIDS (N = 654), Percent*

Advice	Area		Other SMSA	Non-SMSA	Total
	Los Angeles	San Francisco			
Use condoms	50	57	50	53	52
Reduce number of partners	64	59	72	48	61
Avoid anal intercourse	33	20	30	17	25
Abstain	17	18	11	17	16
Switch to heterosexual life-style	7	13	9	8	9

AIDS = acquired immunodeficiency syndrome, SMSA = Standard Metropolitan Statistical Area

minant of sexual history-taking practices. The finding that adequate sexual histories are taken more often by women physicians is consistent with the data summarized by Morin and Garfinkle[4] that indicate most studies have found that men tend to have more negative attitudes or to feel threatened by gays than women. In a survey of physicians in San Diego, Mathews and co-workers found that younger physicians were less homophobic.[5] In this survey, younger physicians were less discomforted by gay patients and more often took sexual histories.

The associations between attitudes (homophobia) and competency in sexual history-taking and counseling with demographic variables (age and gender) present interesting challenges to those concerned with medical education and control of the spread of AIDS. Early medical school courses in sexual history taking need to be reinforced with specific attention to these skills and those of sexual counseling in residency training. Those physicians whose negative attitudes may reflect an age-cohort effect—that is, a function of prevailing societal values—or to be due to intrapersonal concerns should become aware of their disability. Consistent with the position of the American College of Physicians on AIDS, these physicians can discharge their ethical responsibilities to gay patients by referring them to practitioners who are able and willing to counsel them.[6]

"Counseling" is a term frequently used but seldom well defined. Recent studies by Lewis and associates suggest that operational definitions of this activity are possible and include not only the indications used by physicians for counseling and the techniques or strategies used, but also the intensity of their efforts to persuade patients to alter their behaviors.[7] Despite the importance of counseling, few postgraduate residency training programs provide structured learning experiences for house staff to teach them how to carry out this important function. As indicated by the responses of physicians in this study, counseling often reflects a physician's biases (switch to a heterosexual life-style) or failure to provide specific details of *how* to change a behavior. Those who would effectively counsel their patients must be able to describe in detail the specific desired behavior changes they are advocating and the means of adopting and maintaining these behaviors.

There is some evidence that personal counseling of patients by physicians is an important factor in affecting patients' behaviors with regard to other risk factors.[8] It is time for professional societies and educational institutions to increase their efforts in teaching the skills of sexual history taking and counseling through continuing medical education activities.

Seminars on retroviruses and the results of drug trials with patients with AIDS may be easier to present (and more comfortable to receive). To maximize our efforts to limit the spread of HIV infection, however, it is essential that physicians learn to assess their patients' risks of exposure to HIV and to counsel them appropriately or refer them to someone who can and will.

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Medical Progress

Pathogenesis of Sarcoidosis

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Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The organs that are involved by sarcoidosis include the lungs in which the granuloma is seen in more than 90% of patients to the pituitary, which is only rarely affected. There are many hypotheses as to the cause of sarcoidosis. Some of them rely on the similarities seen between sarcoidosis and the other granuloma-forming diseases such as tuberculosis, berylliosis, pine pollen inhalation and acute and chronic bacterial and viral infections, while others find similarities between sarcoidosis and immune reactions observed in autoimmune disorders. Still other explanations implicate a genetic predisposition or a still-unknown agent as the underlying cause of the granuloma formation.

(Van Gundy K, Sharma OP: Pathogenesis of sarcoidosis. West J Med 1987 Aug; 147:168-174)

What causes sarcoidosis remains a mystery. Despite a significant amount of research, the exact cause and factors that result in granuloma formation remain unknown. We review the typical sarcoid granuloma from its histologic features to the many hypotheses as to its origin. Also reviewed is the typical history of the granuloma from its primary formation to the development of end-stage fibrosis.

Sarcoid Granuloma

On histologic examination a lesion of sarcoidosis is a well-defined round or oval granuloma made up of compact, radially arranged epithelioid cells with pale-staining nuclei (Figure 1). These nuclei appear pale because the growth of the chromatin does not keep pace with the growth of the cytoplasm. The epithelioid cell, a modified macrophage, acquires its name because of its vague resemblance to an epithelial cell. The typical giant cell of the sarcoid granuloma is of the Langhans' type in which the nuclei are arranged in an arc or a circular pattern around a central granular zone. Lymphocytes may be found within the "tubercle" but are usually seen at the periphery. Caseation is absent; occasionally fibrinoid necrosis may be seen.[1] Fibrinoid necrosis is prominent in areas where several granulomas have coalesced and may be distinguished from caseation by the presence of a fine reticulin pattern on silver staining.[2]

What does this organized network of inflammatory cells of different origin guard so zealously? It has been suggested that the shape of a granuloma is the product of a perimeter defense that occurs when the inciting agent is small or circular, as in cases of tuberculosis, histoplasmosis, coccidioidomycosis and talc and beryllium granulomatosis.[3] It is conceivable that the sarcoid granuloma shrouds the mystery of a persistent, poorly degradable "antigen" of low potency. Indeed, this agent, if there is one, has an excellent survival record; it rarely kills the host!

Recently developed monoclonal antibody techniques and indirect immunofluorescence methods have given us a glimpse of the dynamic relationship between the various components of the granuloma and the putative causative agent. The center of the granuloma is composed of macrophage-derived cells and OK T4 helper lymphocytes, whereas the periphery of the granuloma has a large number of antigen-presenting interdigitating macrophages and OK T8 suppressor lymphocytes. The lymphokines from the inflammatory cells recruit blood-borne monocytes, prevent macrophage migration and keep the chronic inflammatory reaction alive and efficient (Figure 2). It is probable that this arrangement of interdigitating OK T8 cells in the periphery and the epithelioid cell-OK T4 pattern in the center does indeed provide an efficient response to a persistent antigenemia. We and others have found this efficient architectural arrangement in cases of tuberculoid leprosy and those in which an efficient immune system keeps the bacillary load to a minimum; in lepromatous leprosy, on the other hand, the arrangement of the immune cells is disorganized and haphazard and bacteria flourish merrily.[4,5]

Natural History of a Sarcoid Granuloma

If a granuloma does not resolve spontaneously or after adequate therapy, it becomes converted into avascular, almost acellular, connective tissue. Granulomas that persist longer than a year or two show peripheral hyalinization and some fibrosis. In late stages complete hyalinization and fibrosis result in tissue scarring.

The mechanisms regulating the development of fibrosis are not well understood,[6] but it stands to reason that if the "antigen" is eliminated, the granuloma will disappear; if it persists, fibrosis will occur. In this drama, alveolar macrophages seem to play an important role by producing a number of active mediators, including a macrophage factor or alveolar macrophage-derived fibroblast growth factor that activates fibroblasts, fibronectin, biologically active factor VII and interleukin-1. The role of lymphocyte products such as interleukin-2 and γ-interferon is unclear. Prostaglandins (PGE_2) appear to modulate fibroblast growth. Neutrophils may be involved in the pathogenesis of fibrosis. The cells are

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ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
HLA = human leukocyte antigen
Ig = immunoglobulin
PG = prostaglandin
SLE = systemic lupus erythematosus

recruited from peripheral blood by a macrophage-derived factor. These lung neutrophils may participate in the development of fibrosis by producing either superoxide anion or by influencing immune complexes.[6]

Organ Involvement and Functional Derangement

No body tissue is exempt from sarcoidosis. Functional disturbances and physiologic abnormalities reflect the organ involvement by the disease and are due to interference of the organ function by the granuloma or fibrosis.

Lungs

The lungs are affected in more than 90% of the patients with sarcoidosis. The pulmonary granulomas have a predilection for peribronchial, subpleural and interlobular septal connective tissue. The alveolar septa when infiltrated with inflammatory cells and fibroblasts become firm and distorted. The blood vessels are involved in as many as 92% of all cases, but clinical pulmonary hypertension is rare. The bronchial and bronchiolar mucosa is commonly involved. Extensive fibrosis in advanced stages results in honeycomb lung and cor pulmonale. Aspergilloma may occur in cystic bronchiectatic cavities or bullous emphysema.

Extensive physiologic studies in the past emphasized functional changes characteristic of "restrictive impairment." Vital capacity, residual volume and total lung capacity are reduced. The loss of diffusing capacity remains perhaps the most common abnormality in sarcoidosis. The diffusing capacity is reduced even in patients with hilar adenopathy without any associated parenchymal infiltrates on chest x-ray film (stage 1).[7] Severe abnormalities of gas exchange also are more frequent than is generally realized. No single test, however, or combination of lung function, arterial blood gas values or pulmonary symptoms can precisely predict exercise limitation in sarcoidosis patients.[8] The obstruction of airways—large and small—is quite common in sarcoidosis.[9,10] The abnormality may result from either one or any combination of the following three factors: endobronchial granulomas and bronchiolitis; fibrosis and disruption of the supporting structure around the airways, or release of chemical mediators, complement products and anaphylotoxins from activated alveolar macrophages. Histamine concentrations in lavage fluid from patients with sarcoidosis are increased. The presence of airways obstruction may indicate persistent and extensive disease.

Lymphatic System

Involvement of the peripheral and other lymph node clusters, such as retroperitoneal nodes, varies from 32% to 78%. For obvious reasons, higher figures for lymph node involvement are observed at autopsy (Figure 3). In lymph nodes the granulomas may replace the whole gland structure or may show patchy involvement with areas of relatively normal lymph node architecture. Lymphatic obstruction a la elephantiasis is extremely rare.

Liver

The liver is palpable in only 20% of patients with sarcoidosis, but granulomas are observed in 63% to 87%, depending on the stage and activity of the disease. The differential diagnosis of hepatic granuloma, particularly in the absence of any

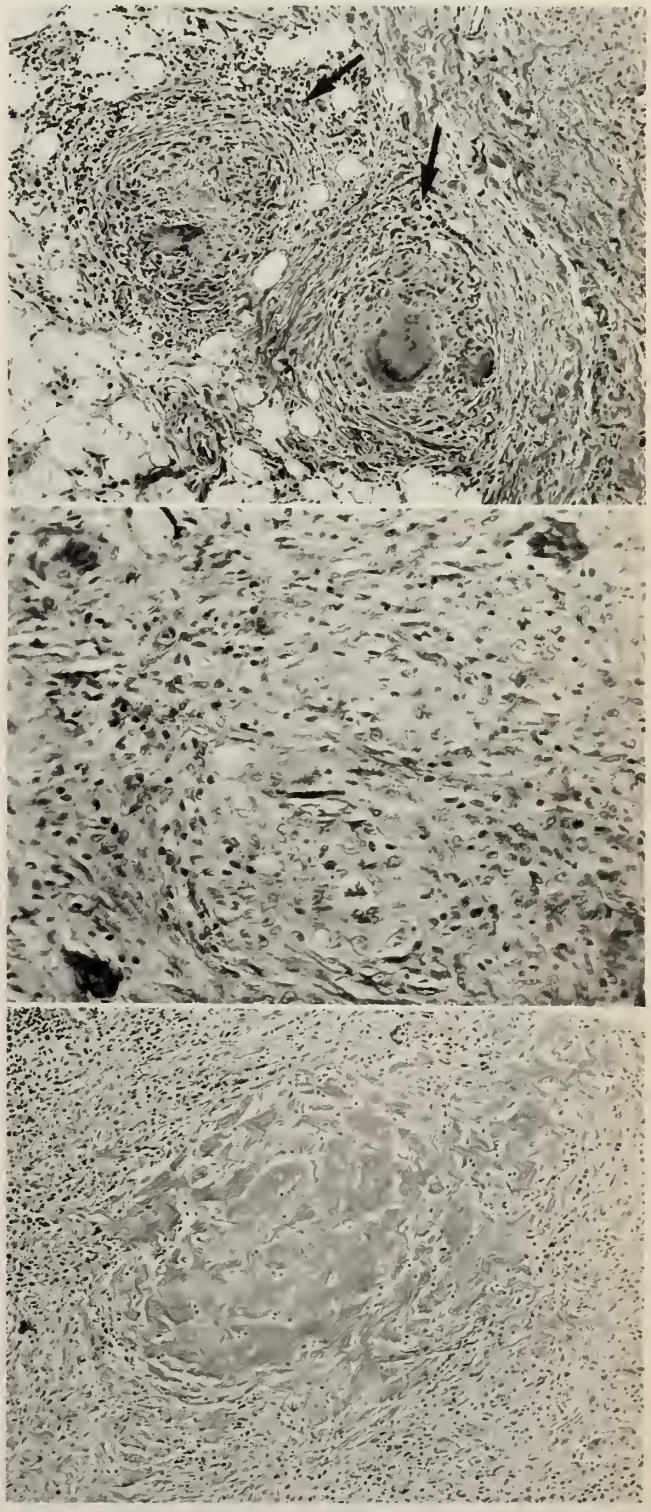

Figure 1.—Top, A sarcoid granuloma shows compact epithelioid cells **(arrows)** with scanty rims of lymphocytes and multinucleate giant cells (hematoxylin-eosin stain, original magnification × 200). **Middle,** An asteroid body is shown inside a granuloma (hematoxylin-eosin stain, original magnification × 200). **Bottom,** The microphotograph shows late-stage granuloma with hyalinization (hematoxylin-eosin stain, original magnification × 300).

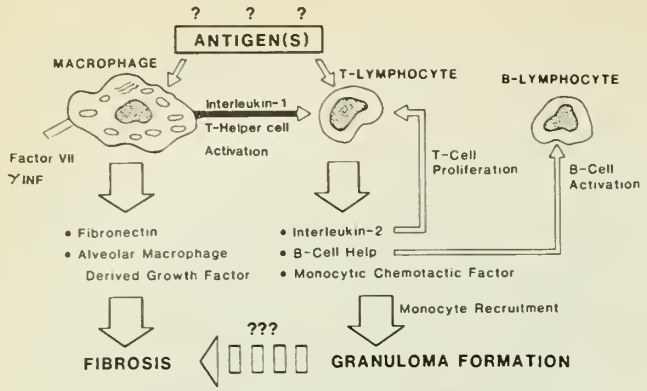

Figure 2.—The schema shows the pathogenesis of pulmonary sarcoidosis. γINF = γ-interferon

evidence of multisystem sarcoidosis, requires an extensive search for acid-fast organisms, other bacteria and fungi, cytomegalovirus, schistosomiasis, primary biliary cirrhosis, lymphoma and neoplastic disorders. Mild elevations of alkaline phosphatase and serum bilirubin levels are common; severe jaundice is infrequent, and portal hypertension is extremely rare (Figure 4).

Spleen

The incidence of a palpable spleen varies from 1% to 42%, but splenomegaly is noticed more frequently at autopsy. Splenic involvement is usually silent; occasionally it may cause pressure symptoms or hypersplenism.

Myocardium

At autopsy myocardial granulomas are found in about a quarter of all patients with sarcoidosis. The granulomas most commonly involve the left ventricular septum. Aorta, pulmonary artery, superior vena cava and pulmonary veins are infrequently affected. The pericardium and the valves are rarely involved. Because of the patchy distribution of the granulomas, an endomyocardial biopsy is of limited value.

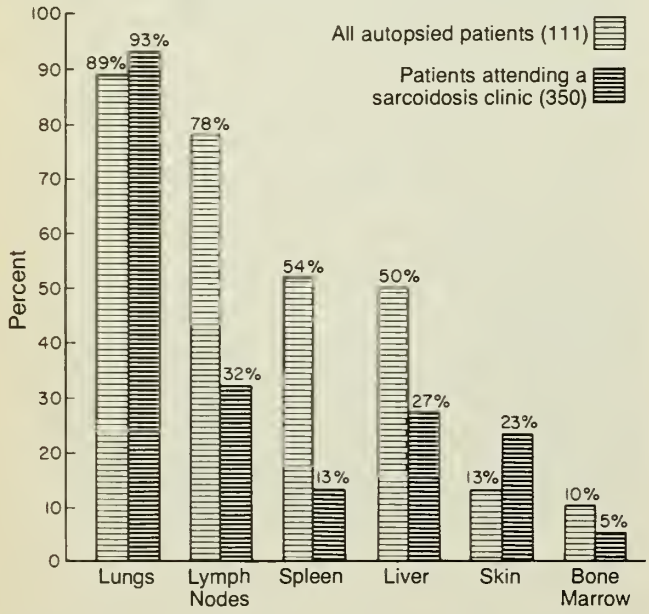

Figure 3.—The graph shows the frequency of various tissue involvement in 111 autopsied cases of sarcoidosis as compared with 350 patients attending the Sarcoidosis Clinic at Los Angeles County-University of Southern California Medical Center.

Eyes

The most common of eye lesions is granulomatous uveitis. Acute uveitis tends to clear spontaneously, but progressive uveal tract inflammation may cause adhesions between the iris and the lens, glaucoma, cataract and blindness. Periphlebitis retinae, retinal hemorrhage, retinitis proliferans, band keratopathy, proptosis and exophthalmos are some of the other uncommon manifestations of ocular sarcoidosis.

Skin

The most specific cutaneous sarcoidosis lesion is lupus pernio. It consists of a raised, violaceous, indurated plaque affecting the nose, the surrounding area of the face and the nasal mucosa. Ulceration is rare.[11]

Other Organs

Almost any organ can be involved. Kidney involvement may lead to the nephrotic syndrome, uremia and renal failure. Hypercalcemia or hypercalciuria may result in nephrocalcinosis or symptomatic renal stones. Bones and joints are affected, but crippling arthritis is uncommon. Sarcoidosis bone cysts are collections of sarcoid granulomas surrounded by a zone of osteoclastic reabsorption. Bone lesions are related to neither serum protein nor calcium levels. Sarcoid granulomas may also be found in meninges, brain substance, hypothalamus, pituitary gland, spinal cord and cranial and peripheral nerves. The rare association of thyroiditis, Addison's dis-

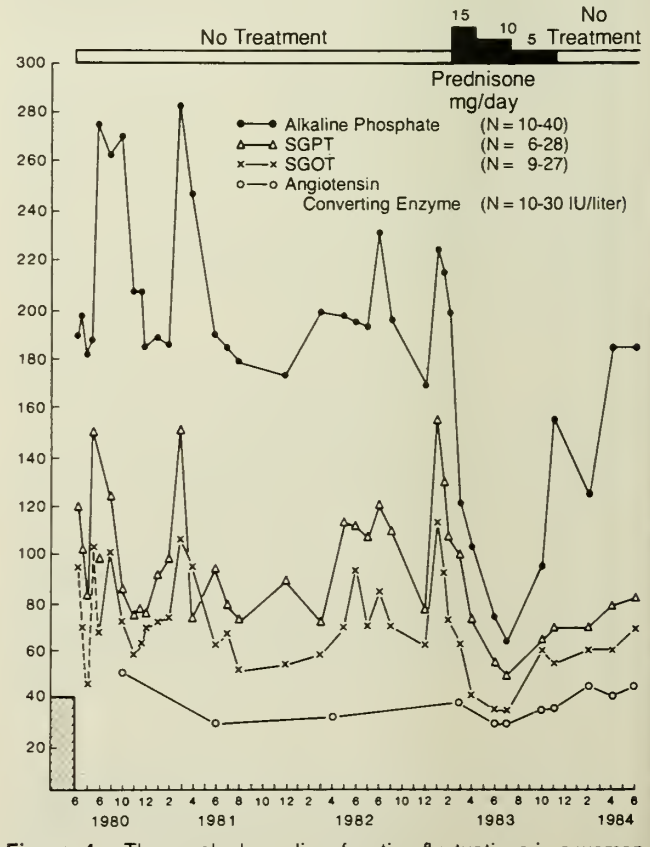

Figure 4.—The graph shows liver function fluctuations in a woman with asymptomatic granulomatous hepatitis. Even a small dosage of prednisone may induce the dramatic normalization of various tests. Mildly abnormal liver function tests in an asymptomatic person do not constitute an indication for corticosteroid therapy. SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvate transaminase

ease, Sjögren's syndrome and sarcoidosis is popularly known as the TASS syndrome.[12]

Cause of Sarcoidosis

What causes sarcoidosis remains a mystery. Hypotheses abound; some are of only historical interest and others merely speculative. Is it a clinical syndrome with many causes, or is it a disease produced by a lone perpetrator? From time to time we have pointed a finger at the following as the etiologic agent of sarcoidosis.

Mycobacterium tuberculosis

The theory of a tuberculous cause of sarcoidosis became popular because of the similarities between the two granulomas and the occasional occurrence of tuberculosis before, during or after the identification of sarcoidosis.[13-16] Bowman and associates, however, failed to isolate bacteria, fungi, *Mycoplasma* or acid-fast organisms from patients with confirmed sarcoidosis.[17] Chapman and Speight suggested that sarcoidosis was a hypersensitivity reaction to atypical mycobacteria.[18] They found elevated antibody titers to atypical mycobacteria in more than 90% of the patients with sarcoidosis. Others have failed to duplicate these findings. Most authorities now agree that there are vast epidemiologic, clinical, radiologic and immunologic differences between sarcoidosis and tuberculosis.[19,20] The theory that sarcoidosis resulted from tissue activation of phage-infected lysogenic mycobacteria never became popular because of the inability of several workers to reproduce the findings reported by Mankiewicz and co-workers.[21-26] Most authorities now agree that the cause of sarcoidosis is neither tuberculosis nor a mycobacteriophage.

Other Infectious Causes of Sarcoidosis

Many known viruses such as mumps, influenza, Newcastle and some uncommon viruses have been implicated as a cause of sarcoidosis.[27-30] Richters and colleagues found ovoid bodies within the mitochondria.[29] They also noted linear densities in the membranes of dilated cisternae that resembled the partial expression of indigenous organisms. Steplewski and Israel cultured biopsy specimens of sarcoid-involved lymph nodes and postulated that the abnormal growth of the fibroblasts suggested that a viral agent was present.[31] In each of these cases, however, the workers were not able to transfer this reaction with supernatant transfer, neither were they able to grow or show true viral activity.[32-34] To this date, there has been no convincing evidence of a viral cause.

Mycoplasma orale has also been found in a greater-than-chance correlation with the incidence of sarcoid.[35,36] The causal relationship still has not been found. Uesaka and coworkers implicated *Nocardia* or an organism similar to it as a possible cause of sarcoid and were able to identify the organism in scalene and mediastinal lymph node specimens from patients who had sarcoidosis.[37] A fungal agent causing sarcoid is a rare phenomenon.

Noninfective Agents

Many noninfective causes of sarcoidosis have been considered. Beryllium was proposed as a cause of sarcoid first by Gentry and associates in 1955 and by several investigators after that.[38-40] The clinical differences between chronic beryllosis and sarcoidosis are many (Table 1). Cummings and Hudgins proposed that inhaling pine pollen was a causal factor in the development of sarcoidosis because the pine pollen induced epithelioid cell granulomas in tuberculin-sensitive guinea pigs.[41,42] Baer proposed that the habit of chewing pine needles was a cause.[43] Other investigators have proposed numerous agents as a cause of sarcoidosis including peanut dust, hair sprays, eating clay, zirconium exposure, mineral oil, talc powder and the use of phenylbutazone, sulfonamide or methotrexate. But in none of these or in others have further epidemiologic studies and investigations been able to substantiate the claims or prove an absolute correlation.[39,40,44-54]

TABLE 1.—*Some Features of Sarcoidosis and Chronic Beryllium Disease*

Feature	*Sarcoidosis*	*Chronic Berylliosis*
Occupational exposure	No	Metal/alloy/ceramics
Onset	Acute or insidious	Insidious
Erythema nodosum	Frequent	No
Hilar lymphadenopathy	Frequent	Rare
Uveitis	20% to 25%	Rare
Granuloma	Noncaseating	Noncaseating
Kveim test	Positive	Negative
Beryllium skin test	Negative	Positive
Angiotensin-converting enzyme	Increased (60%)	Normal
Genetic background	HLA-B8/A1/Cw7/DR3	Not known
Prognosis	Good	Poor

HLA=human leukocyte antigen

Genetic Predisposition

There is an uneven distribution of sarcoidosis throughout the world, with the highest prevalence of the disease among blacks in the United States, Irish and West Indians in London and Puerto Ricans in the New York metropolitan area. This suggests the possibility of some yet-unrecognized genetic and environmental predisposition to the development of sarcoidosis.[55,56]

There is a considerable variance in human leukocyte antigen (HLA) markers associated with sarcoidosis in different parts of the world. Tachibana and colleagues reported an increase in HLA-DR MT2 and HLA-Bw61 in Japanese patients with sarcoid.[57] Thunell and co-workers found an increase in HLA-B8 in patients with erythema nodosum and early sarcoidosis and an increase in HLA-B27 in Swedish patients with advanced sarcoid.[58] Möller and associates could find no association between HLA-B7 phenotypes and sarcoidosis in German patients.[59] Others have been unable to show similar associations or disassociation with various HLA markers.[60-63]

Other environmental factors may influence the occurrence of sarcoidosis such as smoking, which may decrease the risk for sarcoidosis developing, especially in young black women. Harf and colleagues compared the smoking habits of patients with sarcoidosis and found a significant protective effect of smoking.[64] Some studies have reported as high as a fourfold increase in the occurrence of sarcoidosis in nonsmokers as in smokers. There is also an increase in the protective effect of smoking with increasing use. Others have found similar protective effects from smoking but not to the same degree as was reported by Harf and co-workers.

Lawrence and associates found that the percentage of total lymphocytes in a bronchoalveolar lavage (BAL) specimen was significantly reduced in normal smokers but not in pa-

tients with sarcoid who smoked.[65] They also observed that a nonsmoking sarcoid patient's BAL specimen showed a decreased percentage of suppressor (T8) lymphocytes and a decrease in the T4:T8 ratio as compared with normal nonsmokers. Katz and Fauci reported that the total number of lymphocytes in the serum was reduced, with an increase in the proportion of suppressor (T8) lymphocytes in all patients with sarcoidosis.[66] Crystal and colleagues reviewed the BAL specimens of patients with sarcoid and found that there is an increase in the number of activated T lymphocytes within the alveolar structures and that the lung T lymphocytes of patients with sarcoid release mediators such as monocyte chemotactic factor.[67] Others have found that the specimens of BAL from patients with sarcoidosis are significantly higher in such agents as immunoglobulin (Ig) A, C3, α_1-antitrypsin, fibronectin and β_2-macroglobulin. The development of sarcoidosis is perhaps induced or aggravated by some or all of these agents; the mechanism by which this occurs is by the activation of blood monocytes in the lung or by increasing and promoting an inflammatory reaction in the pulmonary system.[68,69]

Autoimmune Disease

Sarcoidosis has at least a partial autoimmune origin.[70,71] Serum IgG values are elevated in 50% of the patients with sarcoid, IgM levels are raised in 25% and IgA levels are elevated in 10%.[72] There are, however, many similarities between sarcoidosis and many of the collagen vascular diseases, especially progressive systemic sclerosis and systemic lupus erythematosus (SLE). In an extensive review of the literature, however, Wiesenhutter and Sharma found only seven reported cases of sarcoidosis coexisting with a collagen vascular disease.[73] Telium reported on the similarity between systemic lupus erythematosus and sarcoid and showed that common to both diseases are hyperglobulinemia and the development of hyalin deposition in the reticuloendothelial system.[71] He also proposed that the development of the granuloma in sarcoidosis is due to the deposition of γ-globulins in response to an immune stimulus. Similar abnormalities have been described in some of the other collagen vascular disorders. Explanations for them have been many, such as a specific defect in the suppressor T cells, permitting the release of a "non-self" clone that causes an organ-specific reaction, abnormal activation of B cells or the abnormal activation of both of these immune systems at the same time.[74] As a further argument that an immune reaction is somehow involved in the formation of sarcoid granulomas is the finding of multiple immunologic changes in many of these diseases. Uveitis is frequently seen in patients with progressive systemic sclerosis or SLE and in 20% to 25% of patients with sarcoidosis.[75-77] As many as 50% of the patients with Sjögren's syndrome have an associated connective tissue disease.[78] Turiaf and Battesi felt that the oculosalivary involvement seen in Sjögren's syndrome can occur in patients with sarcoidosis and at times it may be a subclinical presentation of sarcoidosis.[79] In about 50% of patients with primary biliary cirrhosis, noncaseating granulomas are found. Primary biliary cirrhosis has been reported in conjunction with Sjögren's syndrome, the syndrome of calcinosis cutis, Raynaud's phenomenon, sclerodactyly and telangiectasia and with renal tubular acidosis. Sarcoidosis and autoimmune diseases may have a common origin with Sjögren's syndrome.[20]

Increase in the number of peripheral B lymphocytes and null cells is seen in SLE and sarcoidosis. Cutaneous sensitivity and the lymphocyte response to mitogens (in vitro) are decreased in both SLE and sarcoidosis. A decrease in the number of peripheral T lymphocytes is seen in patients with SLE, progressive systemic sclerosis and sarcoidosis; monocytes are hyperbasophilic and activated in cases of these disorders. A positive antinuclear antibody test is seen in 5% to 30% of patients with sarcoidosis, and a positive rheumatoid factor is seen in 20% to 40% of patients with the disorder. Serum and tissue immune complexes are frequently seen in patients with sarcoidosis, especially if erythema nodosum is present.[72]

Most, if not all, patients with the organ-specific autoimmune disorders, such as Graves' disease, idiopathic Addison's disease, Hashimoto's thyroiditis, Sjögren's syndrome, idiopathic thrombocytopenic purpura, myasthenia gravis, scleroderma and primary biliary cirrhosis, have hyperglobulinemia, which occasionally may coexist with sarcoidosis.[74,80] They also occasionally have nonspecific circulating antibodies and some, if not all, do respond to some extent to corticosteroid therapy, as do patients with sarcoidosis. Additional immunologic disorders that have been associated with sarcoidosis include autoimmune-induced thyroiditis,[81] vitiligo and pernicious anemia.[12,82]

Hematologic abnormalities are common to both sarcoidosis and autoimmune diseases, the most common one being thrombocytopenia.[83,84]

Amyloidosis is rare in patients with sarcoidosis; when it occurs, it may be related to the immune reaction and hypergammaglobulinemia.[85-89] A possible explanation as to why the prevalence of amyloidosis is not higher in patients with sarcoid is that as many as 80% of the patients in whom sarcoid develops will have resolution of their disease in less than two years and thus the disease may not exert a long enough or strong enough antigenic stimulus to induce the formation of secondary amyloidosis.[89]

Sarcoidosis frequently involves the pulmonary vasculature.[90,91] With the pulmonary capillary tunica propria being involved about 50% of the time, the endothelial cells are enlarged in 80% of the patients affected with sarcoidosis, and perivascular edema is seen in 60% of these patients.[92,93] In some with sarcoidosis in whom widespread granulomatous vasculitis develops, the vasculitis itself may play a role in the development of sarcoidosis.

The higher antibody response and immune complexes usually occur in the early acute stages of the disease[94,95] and may actually represent a better prognosis. Further associations between immune diseases and sarcoidosis remain to be proved. There are just as many or more differences between sarcoidosis and autoimmune disorders, including many clinical, radiologic and immunologic ones, that preclude vasculitis or autoimmune disorders as the major causes of sarcoid.

Cancer

Noncaseating granulomas are occasionally seen in patients with certain malignant disorders. Bronchogenic carcinoma was described in 1954 by Jefferson and associates[96] and later reported by others as having many similarities with sarcoidosis.[97-101] Granulomas have been described in patients after radiation therapy and after chemotherapy.[101] Sarcoidosis has occasionally been confused with lymphomas and carcinomas because of radiographic similarities such as bilateral hilar adenopathy.[100,101] There have been a few reports of

the coexistence of Hodgkin's lymphoma or bronchogenic carcinoma and sarcoidosis in the same patient.[102] Although sarcoidosis and Hodgkin's disease have certain common clinical and immunologic features, so far no convincing etiologic relationship has been established.[103-106]

The question as to whether the immunologic defect in sarcoidosis may in some way lead to the development of Hodgkin's disease or that a common virus may induce either of the diseases is still speculative. Brincker and later Brincker and Wilbek found that the incidence of malignant lymphoma was 11 times more common in patients with sarcoidosis than in the general population.[107,108] But studies done by Romer and again by James failed to confirm this increased incidence.[109,110] By applying strict diagnostic criteria with a thorough evaluation of patients, it is relatively easy to distinguish between the granulomas caused by malignant disorders, radiation therapy and chemotherapy and the multisystem disease called sarcoidosis.

Conclusion

There are many unanswered questions about sarcoidosis. In which organ does the disease originate? How does it disseminate? Considerations are that sarcoid spreads through either a hematogenous or a lymphatic route, or that it originates from either a hypersensitivity reaction or a vasculitis. It is possible that the initial alveolar injury that results in the formation of the immune and inflammatory reaction in sarcoidosis is caused by an inhaled antigen. After this stimulus the alveolitis may either resolve or remain dormant indefinitely, or it may become chronic, resulting in persistent granuloma formation and fibrosis. The exact antigen or antigens that cause the initiation of the alveolitis remain obscure, but the formation and perpetuation of the granuloma are carried out by activated T cells. The presence of hyperglobulinemia, defective suppressor T-cell function, loss of self-tolerance to self-antigens with the appearance of autoantibodies, uveitis and the favorable response to immunosuppressive therapy suggest that an autoimmune mechanism plays an important role in the pathogenesis of sarcoidosis. The expression of the sarcoid granuloma may be influenced by hormonal or environmental stimuli. A genetic predisposition or genetic abnormality may play a role in the expression of the disease. Okabe and colleagues have recently shown chromosomal aneuploidy in the granuloma cells.[111] The stimulus for the formation of the aneuploidy chromosomes formation can be speculated as originating from a chromosomal abnormality or the desuppression of opsonin, or it may be due to a bacteriophage that has not yet been isolated. It is conceivable that an environmental agent may stimulate the formation of the aneuploidy cell and the formation of sarcoidosis. On the other hand, it is just as possible that chromosomal aneuploidy may be totally unrelated to granuloma formation.

The pathogenesis of sarcoidosis is still undefined, but with the facilities now at our disposal in the field of electron microscopy, virology and immunology, we should be able to pin down the etiologic agent in the not-too-distant future.

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The Neurologic Sequelae of Cardiac Arrest

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

W. T. LONGSTRETH, Jr, MD:* After trauma and drug overdose, cardiac arrest is the third most common cause of coma in Seattle. Just 20 to 30 years ago, all persons experiencing a cardiac arrest died. Because of technologic developments,[1] patients may now survive but may also suffer brain damage. In this conference I review information concerning the neurologic sequelae of cardiac arrest, concentrating on investigations done at the University of Washington and on Medic I, the prehospital emergency medical system in Seattle. I review the clinical course, prognosis and treatment of coma after cardiac arrest. The discussion of the clinical course and prognosis encompasses both early prognostic factors, including blood glucose level, and later prognostic factors, including cerebrospinal fluid creatine kinase. An important use of the information gained from these studies on complete, global brain ischemia is its possible application to patients with focal brain ischemia. In further discussing this topic, I will focus on decisions that clinicians face concerning limiting medical support.

Clinical Course and Prognosis

The Early Course and Prognosis

Our study population consisted of 459 patients who had suffered out-of-hospital cardiac arrests in Seattle between March 1970 and March 1980, had been resuscitated by Medic I and had been admitted to Harborview Medical Center.[2] Patients who experienced cardiac arrest in a hospital setting were excluded because of a possible difficulty in determining the neurologic outcome specific to the arrest. The major outcome of interest was whether a patient regained consciousness or awakened, as defined by chart documentation of the patient's ability to follow commands or speak comprehensibly. Only patients with well-documented ventricular fibrillation or asystole were considered. Patients in whom cardiac arrest had followed another event, such as respiratory arrest, drug overdose or trauma, that might confound the determination of outcome were excluded. Complete follow-up was obtained for almost all patients.

Overall, 39% of the patients never awakened after cardiac arrest. In these patients, brain death was a rare outcome probably reflecting a greater resistance of the brain than the heart to such insults. Most of the patients who never awakened entered a persistent vegetative state.[3] Of these patients, 80% died during their initial hospital stay. The patient surviving longest in a vegetative state lived more than five years before his final cardiac arrest. Karen Ann Quinlan recently died after about ten years in a persistent vegetative state ("A Long Twilight Comes to an End [Karen Ann Quinlan, Obituary]," *Newsweek*, June 24, 1985, p 81), and a 6-year-old girl who never awoke after her appendectomy survived for 37 years, 111 days.[4]

Of the 61% of our patients who did awake, two thirds had complete neurologic recovery. To identify factors that predict outcome, 27 variables available from the time of admission were examined.[5] Although most of them were significantly related to awakening, none considered alone was pathognomonic. Consequently, we used a multivariable predictive rule.[6] With discriminant analysis, 7 of the 27 variables were found to be significantly related to awakening. After examining several models for complexity and efficiency, we decided on a four-variable rule (motor response, pupillary light response, spontaneous eye movements and admission blood glucose) (Table 1). When these four variables were controlled, the only other items significantly related to awakening were whether the arrest had been witnessed, whether epinephrine had been given during the resuscitation and whether norepinephrine had been given. When all patients not awake on admission after an out-of-hospital cardiac arrest were classified, the potential scores ranged from 0 to 9, and the percentage of patients who awoke varied from 0% to 95% (Table 2).

Other investigators have also examined multivariable predictive rules. In a cooperative study on nontraumatic coma,[7] the subgroup of patients with hypoxic-ischemic coma lasting six hours or more was analyzed.[8] A multivariable technique, recursive partitioning, was used to generate predictions of neurologic outcome at various times after cardiac arrest. This prospective study included a mix of patients with in-hospital and out-of-hospital cardiac arrests and other hypoxic and ischemic brain insults. Despite the different patient population, the initial prediction rule identified the major predictor variables as pupillary light response, motor response and spontaneous eye movements.[8] Thus, both models found similar early clinical predictors of neurologic outcome. Neither predictive rule, however, has been validated in a prospective setting.

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(Longstreth WT Jr: The neurologic sequelae of cardiac arrest [Specialty Conference]. West J Med 1987 Aug; 147:175-180)

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ABBREVIATIONS USED IN TEXT

CK = creatine kinase
CSF = cerebrospinal fluid

Admission Blood Glucose

The importance of the admission blood glucose level as a predictor of neurologic recovery after cardiac arrest deserves further comment. In 1977 Myers and Yamaguchi produced 13 minutes of complete, global brain ischemia with ventricular fibrillation in monkeys.[9] After resuscitation, minimal brain damage was found in all but two animals that showed extensive cortical necrosis. The only difference in protocol was that the two monkeys with severely damaged brains had been given 200 ml of 5% dextrose solution before the arrest and the others had received a saline solution. The importance of the blood glucose level as a determinant of brain damage at the time of a hypoxic-ischemic brain insult has also been shown in animals by other investigators.[10-15] The mechanism for this augmented damage is unknown but may be associated with excessive lactic acid production.[16] When blood stops flowing, glucose metabolism continues anaerobically, and the availability of more glucose at the time of stagnation can cause a greater production of lactic acid. How lactic acid can be linked to cell destruction is unknown but may involve the flux of calcium into the cell.[17,18]

Further evidence for glucose as a predictor of neurologic recovery was found in studies done in patients with focal brain ischemia or ischemic stroke. A direct association has been found between a fasting blood glucose level within 48 hours of admission and severity of the acute stroke as measured by clinical examination and computed tomographic scans of the head.[19] Other investigators have shown that the blood glucose level within 24 hours of admission is significantly related to the percentage of patients who never regain independence.[20]

Whether an elevated glucose level is a cause or an effect of brain damage is an important question raised by the findings in patients after cardiac arrest and ischemic stroke. In an attempt to answer this question, we examined data that had been collected for another study. Serial blood specimens were collected on patients during out-of-hospital cardiac resuscitation mostly in 1977.[21] These data showed that the blood glucose level rose significantly during the resuscitation of patients who died in the field and of those who were admitted and either awakened or never awakened. With the time variable controlled in the analysis, the blood glucose level and awakening state were not significantly related. Unfortunately, the admission blood glucose level in these patients was unknown. Using the duration of cardiopulmonary resuscitation and regression lines summarizing these data, however, the mean blood glucose level at the end of resuscitation was estimated to be 254 mg per dl for those who awakened and 309 mg per dl for those who never awakened. These estimates were similar to actual blood glucose levels found on admission in a previous study: 262 mg per dl for those who awakened and 341 mg per dl for those who never awakened.[22] Thus, the higher blood glucose level on admission in patients who never awaken may simply reflect a longer and more stressful resuscitation. These data do not suggest that lowering blood glucose levels during or after admission would alter the outcome.

Interactions among blood glucose level, duration and ease of resuscitation and outcome remain difficult to examine in patients. Further experiments in animals are needed. Until issues of cause and effect are resolved, however, glucose loading should probably be avoided in patients with or at risk for hypoxic-ischemic brain damage.[14,23]

TABLE 1.—*Rule to Calculate Score That Predicts Awakening**†

Motor Response	+	*Pupillary Light Response*	+	*Spontaneous Eye Movements*	+	*Blood Glucose Level on Admission, mg/dl*
0=Absent		0=Absent		0=Absent		0=≥300
1=Extensor posturing		3=Present		1=Present		1=<300
2=Flexor posturing						
3=Nonposturing						
4=Withdrawal or localizing						

*Modified from Longstreth et al.[5]
†See Table 2 to interpret score.

Later Course and Prognosis

The results from the studies at the University of Washington suggest that the probability of awaking after cardiac arrest falls precipitously during the first four days after arrest (Table 3). Of the 459 patients studied, 279 awakened eventually, giving an overall probability of awaking of .61. By four days after the arrest, however, the probability of awaking was only .14. The population available for awakening was continually being reduced due to patients who awoke or died without awakening. Because deaths occurred more frequently than awakenings after day 4, the probability for awakening actually rose. The last three patients to awaken in this series did so at 56, 75 and 100 days after cardiac arrest.

The degree of neurologic recovery in patients who awakened also varied considerably during the first four days after arrest (Table 4). Of the 279 patients who awakened eventually, the probability for full recovery was .67. The probability of full recovery fell, however, so that after four days, all 14 patients who awakened had some permanent deficits and all six patients who awakened after 14 days had severe permanent deficits that precluded independent living.

These findings may be used to predict neurologic recovery at a particular time after an out-of-hospital cardiac arrest. For example, 142 patients were not awake two days after cardiac arrest and 39 (27%) of those patients eventually awakened (Table 3). Of those 39 patients, 7 (18%) eventually had full neurologic recovery (Table 4). These two probabilities can be multiplied, suggesting that only 5% of patients who are unconscious two days after cardiac arrest awaken and have full neurologic recovery. Multivariable predictive rules that are applicable at later times have been generated from the cooperative study on nontraumatic coma.[8]

Cerebrospinal Fluid Creatine Kinase

The time period between two and three days after cardiac arrest is critical for predicting recovery. During this period a remote possibility of full neurologic recovery still exists, but most of the patients who awaken will have some neurologic deficits and many will have severe deficits. About 80% of the patients still not awake at three days after the arrest will never awaken. An objective measure of brain damage that could be applied in this time interval would be useful. A cerebrospinal fluid (CSF) creatine kinase (CK) level seems well suited to this task. The brain is rich in the BB isoenzyme of CK, skeletal muscle in the MM isoenzyme and myocardium in the

TABLE 2 —*Relation of Score to Actual Awakening**

Score	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Patients with score who awakened, %	0	6	12	29	21	70	75	79	94	95
Grouped scores		*0,1,2*			*3,4*			*5,6,7*		*8,9*
Patients with score who awakened, %		5			24			74		95

*Modified from Longstreth et al.[5]

TABLE 3.—*Probability of Patient Ever Awaking After Out-of-Hospital Cardiac Arrest**

Days elapsed since cardiac arrest	0	0.5	1	1.5	2	3	4	7	14	21
Patients ever awaking after times specified, No.	279	157	80	56	39	21	14	12	6	3
Patients likely to awake, No.	459	281	196	165	142	115	100	66	32	16
Probability of ever awaking	.61	.56	.41	.34	.27	.18	.14	.18	.19	.19

*Modified from Longstreth et al.[2]

TABLE 4.—*Maximal Neurologic Recovery in Patients Awaking After the Times Specified**

Days elapsed since cardiac arrest	0	0.5	1	1.5	2	3	4	7	14	21
Patients ever awaking after times specified, No.	279	157	80	56	39	21	14	12	6	3
Proportion of awakening patients with										
No gross deficits	.67	.50	.26	.25	.18	.14	0	0	0	0
Cognitive deficits	.22	.32	.44	.41	.36	.24	.21	.15	0	0
Motor and cognitive deficits	.11	.18	.30	.34	.46	.62	.79	.85	1.0	1.0

*Modified from Longstreth et al.[2]

MB isoenzyme. When the brain is injured, CK-BB is released from the brain tissue into the interstitial spaces and from there into the cerebrospinal fluid. The amount released is directly proportionate to the amount of irreversibly damaged brain tissue.[24,25] Although the test has little diagnostic usefulness, it might serve as a good prognostic index of the degree of brain damage.

While the University of Washington studies were in progress, other investigators completed a series of detailed studies on CSF CK levels and cardiac arrest.[26,27] Serial determinations indicated that the CSF CK value was substantially elevated in patients who never recovered after cardiac arrest and peaked between 48 and 72 hours after the arrest. No elevation was seen at any time after cardiac arrest in patients with complete recovery. Finally, in patients with evidence of some brain dramage, intermediate values were found. A high degree of correlation between the CSF CK level and the amount of brain damage on neuropathologic examination was also found in patients who died.

Similar results were found in our patients after cardiac arrest in retrospective and prospective studies.[28] In the prospective study, results of the CSF CK determinations were withheld from physicians caring for the patients to avoid influencing decisions concerning degree of medical support. The investigator determining the degree of neurologic recovery was also unaware of the results of CSF CK determinations. We found that the CSF CK was significantly related to the neurologic outcome. Most of our incorrect predictions of awakening in patients who subsequently never awakened could be explained either by additional brain insults that followed CSF sampling, early death before neurologic recovery or early sampling of CSF CK, often less than 12 hours after arrest. Since our initial reports, we have collected about 80 additional specimens of CSF for CK isoenzyme determinations. We now suggest measuring the CK between two and three days after a cardiac arrest. To date, no patient with a CSF CK activity of 150 units per liter or greater has awakened. CSF specimens from control patients without acute brain injuries contain CK activity of less than 5 units per liter.[29] The precise cutoff that will maintain the specificity of the test at 100% remains undefined and may change as our experience with the test grows.

Doing CSF CK electrophoresis in a few of our patients has shown unusual isoenzyme patterns (Figure 1).[30] When specimens are run after adding a mild reducing agent such as dithiothreitol, activities increase due to reactivation of reversibly inactivated CSF CK. In most samples, CK-BB is the predominant isoenzyme. Other isoenzymes are sometimes seen, however. Migrating cathodal to the MM band is a band with the same mobility as that described in the literature for mitochondrial CK. Homogenized brain tissue obtained at the time of autopsy contains both CK-BB and mitochondrial CK.[31] The MM or MB isoenzymes are not found in brain tissue. Because mitochondrial CK is membrane bound, unlike CK-BB which is in the cytoplasm, and because brain tissue contains smaller amounts of it, mitochondrial CK appears in CSF only after severe brain damage. Mitochondrial CK is often found in specimens obtained from patients with brain death.

Another isoenzyme in some CSF specimens has an electrophoretic mobility similar to CK-MB in serum and the same as that described in the literature for a recombination MB. The presence of this CSF isoenzyme may represent a recombination of MM and BB.[30] When the CSF is contaminated with CK-MM from the serum, recombination with CSF CK-BB can occur to yield CK-MB. We have found CK-MB only when CK-BB and MM have had an opportunity to incubate. Consequently, in a case of a traumatic tap where the MM and BB may mix initially, we have not found MB if the specimen is immediately placed on ice and kept at 4°C until

the assay is done. Care should be taken with such contaminated specimens. The total CSF CK level may be elevated, but on electrophoresis the predominant isoenzyme may be due to CK-MM and not CK-BB. If appreciable amounts of MM are detected on electrophoresis, then CSF CK-BB is quantified by using electrophoresis or immunoinhibition techniques.

CSF CK determinations may also be useful in patients with focal brain ischemia, such as that which follows acute, ischemic stroke. As with global brain ischemia, after ischemic stroke, the CSF CK level rises, reaching a peak between two to three days after the stroke occurs.[32-35] Whether the degree of elevation correlates well with the degree of neurologic recovery has not been shown. The isoenzyme pattern might help to locate small strokes because the proportion of BB and mitochondrial CK varies in different regions of the brain.[31]

Treatment

Based on the information presented above, a prognosis for neurologic recovery can be rendered early in the clinical course of patients after cardiac arrest. Ideally, this information would identify patients with the greatest need for treatment. At present, there is no specific, effective treatment for global or focal ischemic brain injury. The duration of complete, global ischemia (from the beginning of cardiac arrest until resuscitation begins) and the duration of incomplete, global ischemia (from resuscitation until a perfusive rhythm is reestablished) are probably the major determinants of brain damage after cardiac arrest. Perhaps the outcomes determined by these insults cannot be altered, but as more is learned about the pathophysiology of brain ischemia, factors may be found that could be controlled after the insult and result in reduced brain damage.

After ischemia, calcium may have a role in the final demise of cells, including brain cells.[17,18] Calcium entry blockers have been proposed as agents to reduce ischemic brain damage,[36] but evidence for a cytoprotective effect of the calcium entry blockers in brain tissue is meager. Some investigators have even shown deleterious metabolic effects of these agents in ischemic brain.[37] Calcium entry blockers have been extensively evaluated in experiments in animals for the treatment of global brain ischemia. Many of the early investigations are difficult to interpret because of differing methods and conflicting results. In a recent study using a primate model, however, it was suggested that nimodipine may have a beneficial effect.[38] Complete, global brain ischemia was produced in pigtailed monkeys and then flow was reestablished. Five minutes after reestablishment of flow, one group was treated with parenteral administration of nimodipine and the other with placebo. Nimodipine is a new calcium entry blocker with potent and selective actions on cerebral vasculature. The animals were then observed for 96 hours and scored according to their neurologic recovery. Significantly better recovery occurred in the nimodipine-treated compared with the placebo-treated monkeys.

Despite these encouraging results, some investigators have suggested that further studies are needed to confirm the beneficial effects of the calcium entry blockers in ischemic brain injury and to define better the protective mechanism.[39] In part, caution has been recommended because of the experience with barbiturates in brain ischemia. In early experiments with animals, barbiturates had also been shown to have a beneficial effect,[40] but a cooperative clinical trial with thiopental loading after cardiac arrest was done and no benefit was found.[41] When the experiments were repeated, the beneficial effects of the initial studies could no longer be shown.[42] Nevertheless, clinical trials evaluating calcium entry blockers in ischemic brain disease are already underway through an international, cooperative, National Institutes of Health-supported trial of the calcium entry blocker lidoflazine.

Calcium entry blockers have also been used in patients with acute ischemic stroke.[43,44] Nimodipine-treated patients fared significantly better than placebo-treated patients when the nimodipine was given orally in a divided dose of 120 mg a day. Both a single-blind study and a recent double-blind study have shown similar beneficial effects. Further clinical investigations of the calcium entry blockers in acute ischemic stroke are needed to confirm these promising results. Other treatments for ischemic brain disease are under active investigation, but at this time there is no known effective treatment in patients.

Figure 1.—Electrophoresis for creatine kinase (CK) isoenzymes shows the following: Lane 1 is control serum showing CK-MM near the cathode, CK-BB near the anode and CK-MB in between. Lane 2 is cerebrospinal fluid (CSF) from a patient after a cardiac arrest before adding a reactivating agent, dithiothreitol (DTT). Lane 3 is the same CSF specimen after the addition of DTT. Note the increase in CK-BB, the presence of mitochondrial CK migrating cathodal to the MM band and the presence of CK-MB thought due to recombination (from Chandler et al[30]).

Decisions to Limit Medical Support

Clinicians are more often faced with decisions concerning the degree of medical support in patients who do not awaken after cardiac arrest than decisions concerning treatment. Guidelines for these decisions vary from state to state.[45] Some use a judicial approach based on case law, some use a legislative approach and others lack formal guidelines. The judicial approach adopted in Washington State is of interest. The first decision by the Washington State Supreme Court concerning medical support of unconscious and incompetent patients occurred in 1980.[46] When brain death developed in a child, his guardian felt uncomfortable with decisions concerning withdrawal of medical support. Although the child died before the ruling, the court suggested adoption of the Uniform Determination of Death Act, which recognizes both circulatory and brain death.

At the time, the justices realized that their ruling did not

apply to more difficult situations, such as one in which a permanently unconscious patient is not brain dead. Shortly after the first ruling, such a case arose.[47] Both family and physicians wanted to withdraw medical support, but hospital administrators felt uncomfortable with the decision. The court ruled in a timely fashion that the limitation was appropriate, and the patient died after being disconnected from her ventilator. With that ruling, the court set guidelines for making such decisions. The courts would be involved to varying degrees in all decisions to limit medical support. A guardian would be appointed by the courts and could then make decisions about medical support based on information supplied by a "prognosis board." Even if a close family member was deemed appropriate, this person would have to apply through the courts to be appointed guardian. The prognosis board would consist of the attending physician and two disinterested physicians who must independently conclude that there was no reasonable possibility of the patient returning to a cognitive, sapient state. The courts would be involved further only if disagreement arose.

The next case concerned a middle-aged man who had been severely handicapped all his life, never functioning at a level greater than that of a 1- to 2-year-old child. After suffering a cardiac arrest, he never awakened. His guardian felt uncomfortable with decisions concerning limiting support. A lower court ruled that a guardian could make such decisions and that it could be in the best interest of the patient to have medical support withdrawn. Support was limited and the patient died. The decision was appealed to the state's supreme court to clarify issues raised by the court in its earlier rulings. In the appeal, the supreme court partially reversed its earlier decision thereby reducing the courts' involvement in such situations.[48] It concluded that if an appropriate surrogate decision maker could be identified, there would be no need to apply to the courts to have that person appointed guardian. The need for a prognosis board and unanimous agreement on prognosis remained the same. Any disagreements concerning degree of medical support would require involvement of the courts. In the situation of a patient who had never been competent, a court-appointed guardian would be needed, but the court would not be involved further. This describes the situation based on case law that presently exists in Washington State. In most cases, there is no need to involve the courts.

Other states have adopted a legislative rather than a judicial approach. In Oregon, a case was brought before the courts in which a child was thought to be permanently unconscious. Family and physicians wanted to withdraw medical support. The court was unable to come to a decision, and an attorney was appointed as a friend of the court to collect additional information. After the child died without a court ruling, the attorney took the information that he had collected to the legislature. Eventually a "Right to Die" law was passed. It outlines a process similar to that which exists in Washington State based on case law. The prognosis board is the same, and the search for a guardian or surrogate decision maker is the same, but there is one important difference. If no surrogate decision maker can be found among family members or previously appointed guardians, then the task falls to the attending physicians. Consequently, in some circumstances the attending physician can make unilateral decisions concerning the degree of medical support. Other states have adopted different legislative approaches, including living wills and durable power of attorney.[49]

Conclusion

The clinical course and prognosis of coma after cardiac arrest have been better defined in recent years. This information may be used eventually to identify those patients who might benefit most from treatments designed to reduce brain damage following ischemic insults. At present, such treatment is not available, although several promising avenues of investigation are being explored. The use of the calcium entry blockers in global and focal brain ischemia is currently the most promising approach. More investigations in animals and in humans are needed, however, before these or any other agents become accepted treatments.

At present, though, we are more often faced with decisions concerning the limitation of medical support than with those about treatment. The guidelines to make such decisions vary from state to state and have come into existence either through rulings by the courts on individual cases or, less commonly, by legislation. In a sense, the neurologic sequelae of cardiac arrest are a result of an imperfect technology. None of these patients would have survived 20 to 30 years ago, and the sequelae did not exist. Now some patients survive and have complete neurologic recovery, but the cases of the rest raise pressing medical and ethical questions.

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Medical Staff Conference

New Approaches to Treating Systemic Lupus Erythematosus

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Systemic lupus erythematosus (SLE) continues to plague thousands of Americans and has become the paradigm of an "autoimmune" disease. Much has been learned about its pathogenetic mechanisms through the study of patients and in animal models of SLE, in particular in the New Zealand black/New Zealand white mouse. In this timely review, David Wofsy, MD, brings us up-to-date on the status of a variety of chemotherapeutic approaches to treat patients with SLE and the promise of new modes of therapy using monoclonal antibodies directed against various lymphocyte subsets in animals. Dr Wofsy is Assistant Professor of Medicine at the University of California, San Francisco (UCSF), and is Assistant Chief of Immunology/Rheumatology at the Veterans Administration Medical Center, San Francisco. His own research work in the field forms the basis of suggesting important future strategies for treating SLE.*

DAVID WOFSY, MD:† Recent attempts to develop better therapies for systemic lupus erythematosus can be divided into three broad categories. First, considerable effort has been devoted to refining conventional immunosuppressive therapy with corticosteroids or cytotoxic drugs, or both, to increase efficacy and minimize toxicity. Second, several unconventional therapies have been explored, including plasmapheresis, total lymphoid irradiation and even diet. Third, new strategies have been proposed, based on recent advances in immunology and biotechnology, in an effort to focus therapy directly on the specific components of the immune system that promote autoimmunity. Before reviewing these three areas, it is important to emphasize that many patients with SLE will never need to consider any of them. For these patients, careful monitoring of disease manifestations, giving topical therapy for cutaneous involvement and nonsteroidal anti-inflammatory drugs for musculoskeletal and pleuritic symptoms and conscientious attention to the social and psychological aspects of chronic illness will be sufficient. In this discussion, however, I will focus on patients with more severe lupus requiring more aggressive therapy because these patients have undergone the most intensive investigation, these are the cases in which the unique training and expertise of physicians are most critical and these people have the most at stake.

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A review of the SLE literature for the past 40 years provides an encouraging picture of a steady improvement in prognosis (Figure 1). Before 1950, SLE was widely considered to be a rapidly progressive terminal illness.[1] This view changed between 1950 and 1970, when several large series described five-year survival rates of 70% to 75% (compared with 30% before 1950) and ten-year survival rates of 50% to 60%.[2-5] This apparent improvement may have been in part artifactual because improved serologic techniques during this period undoubtedly facilitated recognition of some cases of mild lupus erythematosus that would previously have gone undiagnosed. In addition, advances in general medical care, particularly the development of better antibiotics, may have contributed to the improved life expectancy. These factors notwithstanding, the introduction of corticosteroid therapy in the early 1950s is generally credited with having played a major role in the improved prognosis. More recent series describing patients followed during the 1970s showed continued improvement in prognosis, with as many as 90% having five-year survival and 80% ten-year survival.[5,6] The basis for this continued improvement was not entirely clear, but it most likely reflected a combination of factors, including a more judicious use of corticosteroids, the selective use of cytotoxic drugs, better antihypertensive and antibiotic medications and the widespread availability of hemodialysis.

Based on the encouraging data in Figure 1, one might have predicted that the 1980s would have brought the legitimate expectation of a favorable prognosis for all patients with SLE. On more careful consideration, however, these data also suggest some of the factors that have complicated clinical research in this area and that have impeded further improvement in prognosis. From a purely statistical viewpoint, these factors can best be summarized by observing that we have reached a point of diminishing returns. That is, now that ten-year survival exceeds 80%, it is necessary to study a large number of patients for a long time if we hope to show a statistical advantage for any new therapeutic approach. This is particularly difficult in a disease like SLE because it is not common and because the diversity of clinical manifestations makes it difficult to assemble a large number of well-matched subjects for controlled clinical trials. For these reasons, there has been only one large controlled therapeutic trial in SLE during the past decade. This trial, conducted at the National Institutes of Health (NIH), tested the hypothesis that combined therapy with cytotoxic drugs and prednisone is better

(Wofsy D: New approaches to treating systemic lupus erythematosus [Medical Staff Conference]. West J Med 1987 Aug; 147:181-186)

ABBREVIATIONS USED IN TEXT

EPA = eicosapentaenoic acid
IV = intravenous
NIH = National Institutes of Health
SLE = systemic lupus erythematosus
TLI = total lymphoid irradiation
UCSF = University of California, San Francisco

than the use of prednisone alone in treating people with lupus nephritis.[7] The results of this study are discussed below.

Cytotoxic Drugs

The NIH study of cytotoxic drug therapy consisted of a prospective analysis of 107 patients with documented lupus nephritis who were randomly assigned to five treatment groups. In the first group, patients received high doses of prednisone alone (1 mg per kg of body weight per day initially, followed by gradual tapering as tolerated). The other four groups tested four different cytotoxic drug regimens, each supplemented by low doses of prednisone (<0.5 mg per kg per day) as needed to treat extrarenal manifestations of systemic lupus erythematosus. In two of these groups, patients received high-dose oral cytotoxic drug therapy with either azathioprine or cyclophosphamide (4 mg per kg per day initially, then gradually tapered as tolerated). A third group of patients received combination chemotherapy with low doses of both azathioprine and cyclophosphamide (1 mg per kg per day of each drug). This regimen was based on principles adopted from cancer chemotherapy in which agents that differ in their mechanism of action may achieve synergistic therapeutic effects while minimizing the toxicity associated with using either agent alone. The final group of patients received intravenous infusions of cyclophosphamide every three months (0.5 to 1.0 gram per sq m of body surface area). This regimen was based in part on studies of animals indicating that intermittent pulse therapy with cyclophosphamide is more effective than daily administration of cyclophosphamide in murine lupus (reviewed by Balow and co-workers)[8] and in part on the hope that intermittent therapy would minimize the risk of bladder toxicity and late malignant complications. Patients in this group were admitted to hospital to receive cyclophosphamide, hydrated intravenously to ensure rapid clearance of the drug from the kidneys and monitored closely to establish a dose of cyclophosphamide that would result in a leukocyte cell nadir of 2,000 to 3,000 cells per μl seven to ten days after the cyclophosphamide infusion.

Renal failure developed more frequently in patients treated with prednisone alone than it did in any of the other four groups (Figure 2). This is consistent with a recent pooled

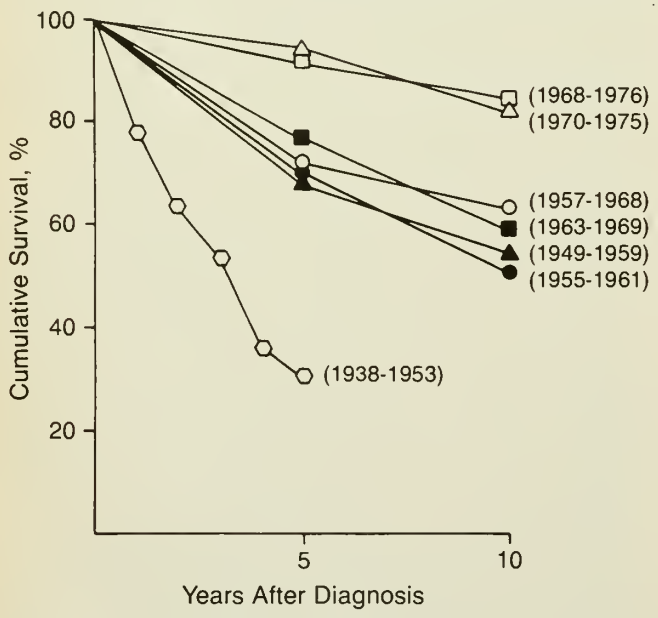

Figure 1.—A composite analysis shows the improved prognosis for patients with systemic lupus erythematosus followed at major referral centers. The studies originated at the following centers: Columbia-Presbyterian Medical Center (Jessar et al, 1938-1953),[1] Cleveland Clinic (Kellum and Haserick, 1949-1959),[2] Sweden (Leonhardt, 1955-1961),[3] New York University (Urman and Rothfield, 1957-1968),[4] Columbia-Presbyterian Medical Center (Estes and Christian, 1963-1969),[5] University of Connecticut (Urman and Rothfield, 1968-1976)[4] and Johns Hopkins University (Feinglass et al, 1970-1975).[6]

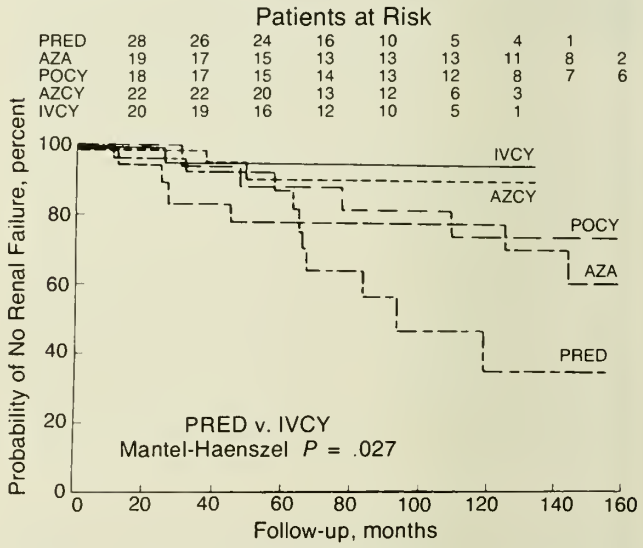

Figure 2.—Probability of maintaining life-supporting renal function in patients with lupus nephritis treated with either prednisone (PRED) alone, high-dose azathioprine (AZA), high-dose oral cyclophosphamide (POCY), combined low-dose azathioprine and cyclophosphamide (AZCY) or intravenous pulses of cyclophosphamide (IVCY). See text for details of therapeutic regimens (slightly modified from Austin et al,[7] with permission).

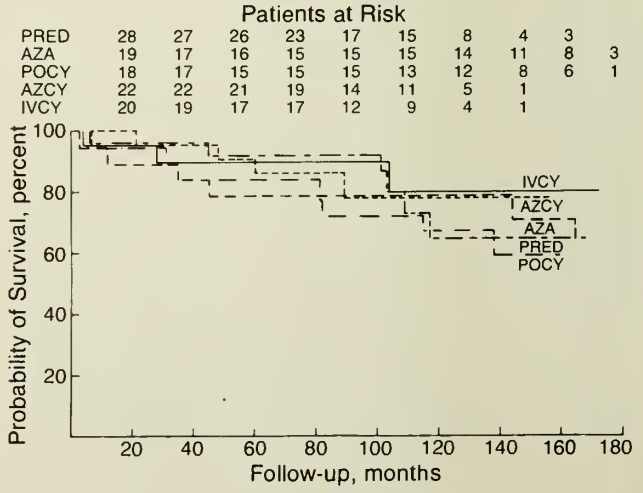

Figure 3.—Probability of survival in patients with lupus nephritis treated with either prednisone (PRED) alone, high-doze azathioprine (AZA), high-dose oral cyclophosphamide (POCY), combined low-dose oral azathioprine and cyclophosphamide (AZCY) or intravenous pulses of cyclophosphamide (IVCY) (from Balow et al,[8] with permission).

TABLE 1.—*Complications of Immunosuppressive Therapy for Lupus Nephritis**

Complication	Treatment Group† PRED	AZA	CY	AZA+CY	IVCY
	% of patients				
Infections					
Major	29	10	17	14	10
Herpes zoster‡	7	10	33	32	25
Premature amenorrhea§	8	18	71	53	45
Hemorrhagic cystitis	0	0	17	14	0
Malignancy	0	16	17	0	0

*Adapted with permission from Balow et al.[8]

†PRED=the use of prednisone alone; AZA=azathioprine; CY=oral cyclophosphamide therapy; AZA+CY=combined oral administration of azathioprine and cyclophosphamide; IVCY=intravenously given cyclophosphamide.

‡$P<.05$ (χ^2), comparing prednisone and azathioprine therapies with the three cyclophosphamide regimens.

§$P<.01$ (χ^2), comparing prednisone and azathioprine therapies with the three cyclophosphamide regimens.

analysis of data from several studies suggesting that cytotoxic drugs may add to the beneficial effects of prednisone.[9] The only group, however, that achieved a statistically significant advantage over the use of prednisone alone with regard to renal function outcome was the group of patients who had been treated with intravenous pulses of cyclophosphamide.[7] After a median follow-up period of seven years, renal failure developed in 43% of patients treated with prednisone alone, compared with only 5% of patients treated with intravenous administration of cyclophosphamide. Despite these encouraging results regarding kidney survival, patient survival was virtually identical in all five groups (Figure 3).[8] Moreover, the toxicity of cytotoxic drug therapy was substantial (Table 1).

Major infections, defined as infections requiring admission to hospital, occurred with similar frequency in all five groups. Herpes zoster infections also occurred in all of the groups, but they occurred with significantly greater frequency in the three groups that received cyclophosphamide. Premature amenorrhea also was strongly associated with cyclophosphamide therapy. This complication occurred in more than 70% of the women who received high doses of cyclophosphamide daily and in about 50% of the women treated with either low doses of cyclophosphamide daily or intermittent intravenous pulses of cyclophosphamide. Hemorrhagic cystitis occurred only in the patients who received oral cyclophosphamide therapy. This observation supports the hope that this complication will not occur in patients treated with intermittent intravenous administration of cyclophosphamide, but the numbers are still too small and the follow-up too short to be certain of this conclusion. The most disturbing observation concerns the frequency of malignancy in patients treated with high daily doses of either azathioprine or cyclophosphamide. After a median follow-up of only 12 years, malignant lesions have developed in 3 of 19 patients treated with high doses of azathioprine and 3 of 18 patients with high doses of oral cyclophosphamide. These include chronic myelocytic leukemia in a 45-year-old woman treated with azathioprine, transitional cell carcinoma of the bladder in a 31-year-old woman treated with cyclophosphamide and polycythemia vera in a 21-year-old man treated with cyclophosphamide.[8] The nature of these malignant disorders strongly suggests an association with cytotoxic drug therapy. Thus far, no cancers have occurred in the patients treated with low-dose combination chemotherapy or with intravenously given cyclophosphamide. But it is much too early to conclude that these regimens will not also be associated with an increased risk of malignancy.

In discussing cytotoxic drug therapy for lupus nephritis at a UCSF Medical Staff Conference ten years ago, Wallace V. Epstein, MD, concluded that "probably the only statement generally accepted is that the use of cytotoxic agents in the treatment of lupus nephritis must be regarded as investigational."[10] Based on the results of the NIH study of cytotoxic drug therapy, it appears that Dr Epstein's conclusion still applies today. Under these circumstances, it is not surprising that several alternative approaches to the treatment of lupus nephritis have been advocated in recent years. Some of these alternatives are reviewed in this article.

Methylprednisolone Pulse Therapy

High-dose intravenous pulses of methylprednisolone sodium succinate were used initially to prevent renal allograft rejection[11] and subsequently to treat idiopathic rapidly progressive crescentic glomerulonephritis.[12] Favorable results in these situations and the expectation that intermittent corticosteroid therapy would be safer than daily therapy have led several investigators to examine the effects of methylprednisolone pulse therapy in patients with systemic lupus erythematosus.[13-17] Although case reports and uncontrolled trials support the contention that this therapy may be effective,[13-15] there has been only one controlled trial to evaluate methylprednisolone pulse therapy for lupus nephritis.[16] In this small study, nine patients receiving conventional daily steroid therapy were randomly assigned to receive in addition monthly pulses of either methylprednisolone (1 gram given intravenously [IV] on three successive days once a month for a year) or a saline solution. At follow-up, the five patients treated with methylprednisolone had better renal function than the control patients, but the very small number of patients studied limited interpretation of the results. Preliminary reports describing a larger controlled trial conducted at University College Hospital in London have shown no advantage for high-dose pulses of methylprednisolone (1 gram given IV on three successive days) over smaller pulses of the drug (100 mg given IV on three successive days).[18] In addition, there is mounting evidence that methylprednisolone pulse therapy may not be as safe as had been hoped. Complications of this therapy in patients with rheumatic diseases now include serious infections in the immediate postpulse period, cataracts in patients who did not receive daily steroid therapy, glucose intolerance, hypertension, fluid retention, gastrointestinal disturbances and central nervous system disturbances.[19] In view of these findings, it is difficult to define the circumstances in which the possible benefits of methylprednisolone pulse therapy outweigh the possible risks.

Plasmapheresis

The use of plasmapheresis in treating systemic lupus erythematosus rests on the tenet that circulating immune complexes and autoantibodies initiate tissue damage in patients with this disorder. This tenet suggests that, by removing circulating immune complexes or autoantibodies (or both), plasmapheresis might inhibit critical pathogenetic mechanisms. Like methylprednisolone pulse therapy, the use of plasmapheresis is supported by several case reports but not yet by controlled studies.[20-25] The only controlled trial of plasmapheresis in patients with SLE consisted of a very short period

(two weeks) of using either plasmapheresis or sham pheresis in patients with mild disease.[23] Although this study showed no benefit from plasmapheresis, the results do not preclude the possibility that more extended therapy in more severely ill patients might be beneficial. It is important to emphasize, however, that plasmapheresis therapy is not a substitute for conventional immunosuppressive therapy, but rather must be combined with other forms of therapy to prevent rebound increases in immune-complex and autoantibody levels.[23-25] For this reason, the considerable expense and risks of plasmapheresis therapy must be added to the risks inherent in other therapies. For plasmapheresis, these include constitutional symptoms (fever, chills, myalgias), potentially life-threatening vascular access problems (sepsis, thrombosis) and cardiovascular complications (hypotension, arrhythmias, myocardial infarction).[24-26]

Total Lymphoid Irradiation

Two years ago, Strober and associates[27] reported successful treatment of intractable lupus nephritis with total lymphoid irradiation (TLI). This approach was based on extensive experience in patients with Hodgkin's disease, in whom TLI had been relatively well tolerated and in whom it had caused prolonged immune suppression.[28] The use of this treatment was further supported by studies in animals indicating that murine lupus could be arrested by treatment with TLI.[29] In an uncontrolled feasibility study, ten patients with severe lupus nephritis underwent TLI.[27] Pretreatment evaluation showed nephrotic levels of urine protein and serum albumin, high concentrations of anti-DNA antibodies and hypocomplementemia (Table 2). Despite these severe abnormalities, TLI was followed by a significant decline in proteinuria, normalization of serum albumin levels, reversal of hypocomplementemia and a reduction in the concentration of anti-DNA antibodies (Table 2). None of the patients had a significant deterioration in renal function after a median follow-up period of 15 months after the radiation therapy, and the mean prednisone dose had been reduced from 36 mg per day before treatment to 16 mg per day at follow-up.

Complications of total lymphoid irradiation were common in the study described above, but they did not result in serious consequences.[27] All patients had constitutional symptoms during TLI (fatigue, nausea, vomiting, weight loss). In addition, xerostomia, marrow suppression and herpes zoster complicated therapy in some patients. The possibility of late adverse sequelae, such as malignancy, was not resolved by this feasibility study. Of greater immediate concern, however, is a recent report of TLI therapy for systemic lupus erythematosus that failed to reproduce the initial encouraging results.[30] Ben-Chetrit and colleagues[30] used total lymphoid irradiation to treat two patients with severe SLE. Severe leukopenia and gram-negative septicemia developed in the first patient during therapy, followed by progressive renal deterioration leading ultimately to end-stage renal disease. Bronchopneumonia and progressive nephritis developed in the second patient, and the patient died two weeks after completion of the radiation therapy. At the present time, therefore, the use of TLI in the treatment of systemic lupus erythematosus should be considered strictly investigational.

TABLE 2.—*Effects of Treatment With Total Lymphoid Irradiation**

Laboratory Values and Treatment	*Pretreatment†*	*Follow-up‡*
Urine protein, grams/24 h	6.9	3.1§
Serum albumin, grams/dl	2.4	3.7§
Anti-DNA antibody (normal <25), units	61.0	23.0§
C3 (normal 90 to 125), mg/dl	81.0	136.0§
Serum creatinine, mg/dl	1.8	1.4
Prednisone dose, mg/d	36.0	16.0§

*Adapted with permission from Strober et al.[27]
†Mean value immediately before total lymphoid irradiation (10 patients).
‡Mean value at the last visit after total lymphoid irradiation (median follow-up was 15 months).
§$P < .05$ (sign test) compared with pretreatment values.

Diet

In systemic lupus erythematosus as in other chronic illnesses, the failure of conventional medical therapy has fueled interest in the role of diet in modulating disease activity. Traditionally, this topic has received greater attention from the supermarket tabloids than it has from medical journals. Nonetheless, there is some basis for postulating that dietary manipulations can alter the clinical manifestations of chronic inflammatory diseases. Dietary fats provide the substrate for the production of mediators of inflammation via the cyclooxygenase and lipoxygenase pathways. Therefore, alterations in dietary fat content may alter the products of these pathways and thereby modify inflammatory responses.[31] For example, eicosapentaenoic acid (EPA), which is high in dietary fish oil, competes with arachidonic acid for metabolism by cyclooxygenase and lipoxygenase (Figure 4). The prostaglandin, thromboxane and leukotriene products of EPA metabolism differ structurally from the corresponding products of arachidonic acid metabolism and therefore also may differ in their inflammatory and immunoregulatory properties. This hypothesis has been tested in animal models for several human autoimmune diseases. In a mouse model for SLE, a diet high in EPA significantly reduced autoantibody production, retarded renal disease and prolonged life.[32] In a rat model for rheumatoid arthritis, however, a diet high in EPA exacerbated the disease.[33] These observations support the hypothesis that dietary manipulations can influence autoimmune diseases, but they also make it clear that the effects of dietary manipulation may be difficult to predict. This problem is underscored by a recent report indicating that a diet high in

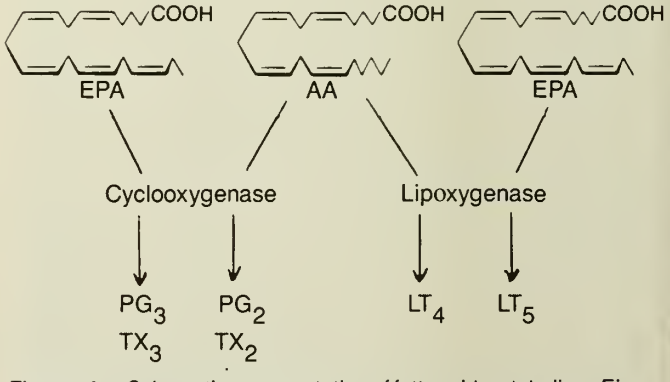

Figure 4.—Schematic representation of fatty acid metabolism. Eicosapentaenoic acid (EPA) competes with arachidonic acid (AA) for metabolism via the cyclooxygenase and lipoxygenase pathways. Because of slight structural differences between EPA and AA, the products of EPA and AA metabolism differ: EPA metabolism produces the prostaglandin 3 (PG_3), thromboxane 3 (TX_3) and leukotriene 5 (LT_5) series of biologic mediators; in contrast, AA metabolism produces the prostaglandin 2 (PG_2), thromboxane 2 (TX_2) and leukotriene 4 (LT_4) series of biologic mediators. The different products of EPA and AA metabolism can have different biologic effects.

EPA may be beneficial in people with rheumatoid arthritis even though it was harmful in rats.[34]

Practical Conclusions

Faced with the sometimes inadequate, sometimes discouraging, data reviewed above, how should we approach the treatment of lupus nephritis in our patients? One principle is evident from the accumulated data: no new therapy is clearly preferable to prednisone alone for routine use in patients with lupus nephritis. Consequently, it would be important if there were some means to prospectively identify subgroups of patients in whom more aggressive therapy would be advantageous. Unfortunately, this goal has not been achieved, despite many attempts to determine whether certain serologic or histologic patterns can be used to predict therapeutic requirements.[35-42] It is beyond the scope of our discussion to review thoroughly this controversial area. From a purely practical standpoint, however, it is possible to make two generalizations from the abundant literature regarding this matter. First, although certain serologic abnormalities correlate with adverse outcomes,[35] no study has established serologic criteria that can be used to identify patients who are likely to benefit from any particular form of therapy. Similarly, although certain renal biopsy findings correlate with the clinical outcome, the histologic appearance of a biopsy specimen does not dictate what therapy is likely to be most effective.[37-40] Therefore, at present we cannot rely on serologic or histologic criteria to establish which therapeutic regimen will be best.

We are left, then, to find some other basis for choosing between several imperfect regimens when daily corticosteroid therapy is ineffective or unacceptably toxic. Often the choice is dictated by the distinct features of individual cases. For example, a history of steroid-induced psychosis would be a relative contraindication to using pulses of methylprednisolone; the desire to maintain fertility would be a relative contraindication to using cytotoxic drugs. The conventional approach has been to add an oral cytotoxic agent when the use of prednisone alone fails. This approach has the advantage that it is relatively convenient for patients and for physicians. At UCSF, we have tended to use chlorambucil rather than cyclophosphamide as the oral cytotoxic agent of choice, in the belief that these two alkylating agents have comparable efficacy and with the confidence that the toxicity of chlorambucil does not include hemorrhagic cystitis or bladder neoplasia. As an alternative to oral chlorambucil therapy, it has been tempting in recent years to administer pulses of cyclophosphamide intravenously in some patients. The appeal of this regimen lies in the NIH data supporting its efficacy and in the hope, supported by preliminary data, that intermittent pulses of cyclophosphamide will be less likely than oral cytotoxic therapy to cause late malignancy.[9]

In general, it is easier to justify the use of cytotoxic agents in older patients. Secondary amenorrhea is a less serious consideration in women who are past their reproductive years. In addition, older patients face fewer years of possible vulnerability to secondary malignant disorders. Accordingly, it is in younger patients that methylprednisolone pulse therapy may sometimes be a more attractive third alternative. Although some advocate the use of plasmapheresis in patients with systemic lupus erythematosus, I believe that plasmapheresis, like total lymphoid irradiation, is still an experimental therapy that should be reserved for consideration in desperate situations or for evaluation in controlled trials.

Future Directions

While further clinical trials may help to settle some of the unresolved issues concerning current therapies for lupus, there is also reason to hope that these forms of nonspecific immune suppression will ultimately be replaced by newer therapies that are focused more directly on the specific components of the immune system that promote autoimmunity. Several strategies for achieving this goal were reviewed recently in this journal[43] and are based on the concept that an immune response reflects a series of interactions involving several cell types, any one of which could be the target of specific therapy. Such therapy might consist of lymphokines that regulate the function of specific lymphocyte subsets, or it might involve monoclonal antibodies that recognize unique surface antigens on specific lymphocyte subsets. For example, humoral immune responses involve not only antibody-producing B cells, but also regulatory T cells and stimulatory antigen-presenting cells, such as macrophages. Thus, it might be possible to suppress production of selected autoantibodies by using monoclonal antibodies that recognize the B cells that produce the autoantibodies, the T cells that regulate their production or the antigen-presenting cells that initiate the response. In fact, all of these approaches are currently under investigation and have shown promise in murine models for SLE.[43-46] Seaman and I have shown that severe lupus nephritis in New Zealand black/New Zealand white mice can be reversed by treatment with monoclonal antibodies to the L3T4 antigen on "helper/inducer" T cells.[44] This approach is supported by recent studies indicating that monoclonal anti-T-cell antibodies can be used successfully in humans to suppress renal allograft rejection.[47] Hahn and Ebling have shown that murine lupus nephritis can be retarded by treatment with monoclonal antibodies that recognize idiotypic determinants expressed by B cells that produce anti-DNA antibodies.[45,48] This approach is supported by recent studies indicating that a limited number of idiotypes is shared by anti-DNA antibodies found in the kidneys of people with lupus nephritis.[49] Finally, Adelman and co-workers have shown that murine lupus can be retarded by monoclonal antibodies directed against class II major histocompatibility antigens on antigen-presenting cells.[46] Recent studies have indicated that certain class II major histocompatibility antigens, such as human leukocyte antigen DR2, are associated with SLE.[50,51] These promising studies in murine lupus provide hope for the development of revolutionary new therapies for people with systemic lupus erythematosus.

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Epitomes
Important Advances in Clinical Medicine

Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

New Developments in Diagnosing and Treating Erectile Impotence

THE UNDERSTANDING of erectile physiology and the treatment of erectile dysfunction continue to be dynamically expanding areas of urologic knowledge.

With a better understanding of the physiology and more sophisticated testing techniques, it has been determined that in 85% of men with impairment for more than a year, there is an organic origin (as opposed to 90% a psychological one, as believed historically).

Organic impotence is due to "failure to initiate" (neurogenic), "failure to fill" (arteriogenic) or "failure to store" (corporal venous leakage). Diagnostic tests are directed toward identifying which of these is the origin so that the most desirable therapy can be selected.

Failure to initiate (neurogenic cause) is generally nonreversible, though the lack of neurologic initiation can be overridden by direct intracorporal pharmacologic stimulation (papaverine hydrochloride and phentolamine mesylate).

Intracorporal pharmacologic stimulation can also be successful in cases of "failure to fill" (atherosclerotic occlusive disease) because the long duration of the stimulus results in filling even with diminished flow. It can also be successful with "failure to store" because the stimulus creates enough flow and tumescence to reduce the venous leak.

Failures to fill and to store are both amenable to a reconstructive vascular operation, which has received a great deal of attention as the procedures—arterial revascularization and venous leak ligation—have shown increased success.

Patients with venous leak or "failure to store" present an especially interesting problem. They most often have had trauma, atherosclerotic occlusive disease or Peyronie's disease. To establish the diagnosis, a new test—dynamic infusion cavernosometry and cavernosography—was developed. Constant penile infusion is done during pharmacologically induced (papaverine and phentolamine) tumescence that should approximate the physiologic state of maximal corporovenous occlusion. If the corporal body pressure falls by more than 30 mm of mercury in 30 seconds (from a beginning pressure of more than 150 mm of mercury), it is diagnostic of a venous leak. The location of the leak is then identified radiographically by intracorporal infusion of dilute radiopaque contrast solution so that the most appropriate surgical procedure can be selected. The procedures of venous ligation, reduction cavernoplasty or dorsal vein arterialization (Virag V operation) have about 60% success in restoring normal erections.

For those whose erectile function cannot be satisfactorily restored using nonoperative means, a reconstructive vascular operation offers an alternative to penile prosthesis, particularly for those patients who are concerned emotionally about the idea of an "artificial erection" produced by a prosthesis.

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The Continent Urinary Diversion

THE SEARCH FOR A satisfactory urinary diversion has intrigued and plagued urologists for more than a century. Ideally such a diversion should duplicate the function of the bladder in being able to effectively collect and store urine without an external appliance, permit emptying under voluntary control, preserve renal function and maintain an optimal quality of life.

The most popular urinary diversion has been the refluxing ileal conduit, which requires an external collecting appliance. For many years the search has continued for a more desirable diversion. Not only do patients with ileal conduits have a high frequency of late complications (chronic pyelonephritis, stones and renal failure) from long-standing reflux, but the psychosocial stigma associated with wearing an appliance can have a pronounced impact on body image and may even deter patients from undergoing a needed radical cystectomy.

Over the past decade there has been heightened interest in forms of diversion that prevent reflux and are continent so that the external appliance is eliminated. The success of these diversions has improved with the development of techniques to transform bowel segments into urinary reservoirs and the creation of functioning urinary sphincters. Various diversion techniques have evolved worldwide, differing by the type of

reservoir used, the method of antireflux protection and the continence mechanism. Such names as Kock, Camey, Mainz and Mitrofanoff have been used to identify some of the more commonly done procedures.

The Kock pouch is the most desirable continent diversion because the pressure within the created reservoir remains extremely low, even with volumes of as much as 1,000 ml, and there are no pressure spikes from bowel smooth muscle contraction (a frequent cause of incontinence in other types of continent diversions). Intussuscepted small bowel afferent and efferent one-way nipple valves prevent urine reflux to the kidneys and urine leaking from the pouch. If these valves are not competent, revision may be necessary, though revision rates are decreasing as technical innovations are perfected.

For those patients whose general condition and prognosis permit them to consider the aesthetic and body image advantages of a continent urinary diversion, the Kock pouch appears to be an attractive alternative.

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Ureterorenoscopy

TRANSURETHRAL ENDOSCOPY of the upper urinary tract has become a routine part of most urologic practices. The technical advances of increasingly smaller rigid and flexible endoscopes with high-resolution lenses and channels sufficient for irrigation and the passage of diagnostic and therapeutic instruments have opened the door of nonincisional access to the upper urinary tract. It is obvious that the therapeutic options offered by direct visualization have had the greatest clinical impact. The options include stone extraction, catheter or stent passage and removal of foreign bodies.

Rigid transurethral ureteroscopy is done with instruments varying between 8.5 and 12.5 French. Following dilation of the ureterovesical junction, the ureteroscope is passed through the ureteral orifice and up the ureter under direct vision to the point of interest. Success rates for passage are above 95%, with failures due to anatomic limitations (ureteral angulation or fixation). The successful extraction of ureteral stones has improved dramatically. Initially only 60% of stones could be removed ureteroscopically, but now stones in the lower ureter can be removed in more than 90% of patients, and those in the upper ureter can be considered for removal. Ureteroscopic stone extraction or disintegration complements other forms of nonsurgical stone removal. Stones below the rim of the bony pelvis cannot routinely be treated with current extracorporeal shock-wave lithotriptors or percutaneous methods. But this region, the most common site for ureteral stones to lodge, is ideally located for ureteroscopic access. When a stone is large or resists extraction, transureteroscopic lithotripsy (stone fragmentation) by ultrasonic electrohydraulic or pulsed-dye laser can be done.

Flexible ureteroscopes, available for 25 years, have finally been perfected to a clinically useful state. Those that are not actively deflectable simply follow the ureter and thus are useful more for diagnostic than therapeutic indications. The deflectable flexible ureteroscope just now becoming commercially available promises more frequently successful access to the upper urinary tract and the ability to visualize and obtain a biopsy of peripheral collecting system lesions and extract or disintegrate calyceal stones. Significant complication rates for those with experience have decreased to about 4% with less than 1% of those cases requiring an open surgical procedure. As with any new technique, a learning curve exists, and complication rates will diminish and success rates increase as a surgeon gains experience.

Transurethral ureteroscopic procedures (diagnostic and therapeutic) have become standard clinical practice and have saved many patients the morbidity of open surgical procedures to accomplish the same goal.

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Integrated Management of Urinary Stone Disease

THE SIMPLICITY, efficacy and relative lack of morbidity of extracorporeal shock-wave lithotripsy (ESWL) in destroying kidney and ureteral stones have revolutionized "surgical" treatment methods since it was first introduced in 1980. Urologists now simply place patients in the treatment machine, aim the shock wave via the sighting cross hairs and destroy the stone in less than 50 minutes. Efficacy? More than 80% of patients are stone-free within three months, and fewer than 30% have any significant pain while passing the fragments. Perirenal hematoma, the worst complication noted to date, occurs in 1 of every 400 patients. There are very few other complications of significance. Hence, it is clear that ESWL functions remarkably well.

The success of this procedure and other relatively noninvasive stone-removal techniques (percutaneous nephrostolithotomy and transurethral ureteroscopic lithotripsy) have permitted the elimination of most stones without an open surgical procedure.

Each of these procedures has specific areas of strength where its use is preferable. ESWL is most effective for renal stones, but can be used for ureteral stones above the sacroiliac joint if there is enough fluid around them to transmit the shock wave and permit fragmentation, or if they can be pushed back up into the kidney for disintegration. Percutaneous nephrostolithotomy is used to debulk staghorn stones, to remove those poorly fragmented by ESWL because of hardness (cystine) and to eliminate stones in poorly draining calyces (dependent, or with narrow infundibulae). Transurethral ureteroscopic lithotripsy is addressed in another of this series of epitomes.

Does this mean we need not worry about preventing renal stone disease? Hardly! Even with these new treatment methods, there can be renal compromise from the stone, from the treatment or from complications of either, and it is certain that a kidney will occasionally be irrevocably damaged.

In view of this, it is important that we prevent recurrences whenever possible. Nearly 80% of patients with stones have a definite metabolic abnormality that can be identified and treated. Diseases such as hyperabsorption or renal leak hypercalciuria, hypomagnesiumuria, hypocitruria and so forth re-

spond to treatment in more than 80% of patients—the same rate of stone prevention as is the success rate of the newer methods of surgical treatment of stone.

After a three-month recovery period, the patient has a metabolic evaluation and a preventive program is prescribed that may include increased fluids, dietary advice or drug therapy (or all of these).

While ESWL and the endourologic procedures represent "miracles" of medical technology that significantly reduce morbidity, prevention that avoids morbidity altogether is clearly the best for patients.

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Recent Advances in Diagnosing and Treating Prostatic Carcinoma

PROSTATIC CARCINOMA, the third leading cause of cancer death in men, is completely silent when confined to the prostate. Disappointingly, only 5% to 10% are identified—by digital rectal examination or prostatectomy for obstruction—while curable.

An exciting new technology, transrectal ultrasonography of the prostate, holds the promise of identifying nonpalpable prostate cancer, and ultrasound-guided needle biopsy assures sampling from a suspicious area.

Autopsies of a large number of men who died from other causes have shown silent, unsuspected prostate cancer in 30% of men in their 50s, 35% in their 60s and 70% in their 70s.

With this high incidence, it is clear that much more sensitive screening methods are mandatory if we are to identify many more while potentially curable.

Total prostatectomy remains the treatment of choice for curable prostate cancer because survival exceeds that with external beam or interstitial irradiation and approximates normal age-corrected life expectancy.

The development of a nerve-sparing operation that preserves potency in 70% of patients has, along with the availability of successful penile prostheses, practically eliminated impotence as a major drawback of surgical treatment. Pelvic lymphadenectomy is done initially for staging purposes (no therapeutic value has been shown). If rapid frozen section shows metastasis to nodes, surgical cure is impossible and total prostatectomy is aborted.

Serum prostate-specific antigen is a newly identified, more accurate tumor marker for monitoring tumor burden. Both prostate-specific antigen and serum prostatic acid phosphatase emanate from the prostate cell, so they are a function of neoplastic quantity (not location).

But neoplastic cells that severely dedifferentiate may be unable to produce acid phosphatase, resulting in a spuriously low prostatic acid phosphatase level even with extensive tumor burden. Prostate-specific antigen, generally less affected by dedifferentiation, promises to more accurately reflect the quantity of neoplastic cells. Unfortunately, levels can be elevated in some benign conditions, such as benign prostatic hypertrophy and prostatitis.

Two new permutations of antiandrogen treatment are now available. Leuprolide acetate (Lupron), a luteinizing hormone-releasing hormone agonist, produces "medical orchiectomy" by eliminating luteinizing hormone release, which secondarily eliminates testicular androgen production while preserving the testicles for those who wish to retain them for psychological reasons, and it avoids the increased thromboembolic and cardiovascular complications of estrogen therapy. Drawbacks of leuprolide therapy include its cost (more than $270 a month) and the necessity that it be given subcutaneously by daily injections.

Ketoconazole (Nizoral), the oral anti-*Candida* agent, has been found in higher doses to block cholesterol uptake into the hormone metabolic cycle, resulting in a substantial reduction of androgen and androgen precursors. A dose of 400 mg given three to four times a day suppresses total and free testosterone to far below anorchidic levels and frequently in our patients has elicited an additional substantial remission. The dose can be titrated against testosterone levels, and the occasional case of gastrointestinal intolerance can be controlled with antinausea agents given shortly before the ketoconazole.

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Lasers in Urology

CERTAIN INDICATIONS for using lasers in urology have emerged, whereas areas have been identified in which lasers appear to offer no advantages over alternative treatment. Both carbon dioxide and neodymium-YAG (yttrium-aluminum-garnet) lasers have provided excellent therapeutic and cosmetic results in the treatment of condylomata acuminata of the external genitalia. A neodymium-YAG laser can be used effectively against selected squamous cell carcinomas of the penis, and its use may avoid the need for partial penectomy in some patients. Some of the early promise that lasers showed in the treatment of urethral strictures has not been realized. Also, the currently available wavelengths have not been of benefit in treating prostatic hypertrophy.

Neodymium-YAG laser treatment continues to offer some practical advantages over electrocautery resection in the treatment of superficial bladder cancer. Flexible instruments can be used, bleeding is not encountered, Foley catheters are not used and anesthesia is not necessary in most patients. The impact of lasers on the recurrence rate of superficial bladder cancer remains uncertain.

Minimally invasive bladder cancer can be eradicated through transmural necrosis produced by a neodymium-YAG laser but results in tumors that invade the deep muscle of the bladder are relatively unimpressive. Currently, the use of lasers should not be considered an alternative to doing cystectomy, but may be useful in patients who are not candidates for a radical operation because of advanced age or poor health.

Experience with lasers in treating lesions of the upper urinary tract through ureteroscopes or the percutaneous route is limited. Lasers have been used to extend the margins of resection after a partial nephrectomy for hypernephroma.

A pulsed-dye laser has recently been approved by the Food and Drug Administration for transurethral uretero-

scopic disintegration of ureteral calculi. It offers some advantages over ultrasonic disintegration (can be used through a flexible ureteroscope) and electrohydraulic lithotripsy (no risk of ureteral wall burn).

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Stein BS, Kendall AR: Lasers in urology. Urology 1984; 23(suppl):411-416

Ultrasonography in Pediatric Urology Patients

PEDIATRIC UROLOGY has incorporated many advances and innovations from other disciplines in recent years, and many sophisticated surgical procedures have revolutionized the treatment of such classic urologic problems as hypospadias, bladder exstrophy and spinal dysraphism.

One of these advances from another field has been the development of high-resolution real-time ultrasound techniques, which have afforded multiple benefits to pediatric urologists and their patients. For children, the studies are noninvasive, cause no trauma or discomfort (no needles or catheters) and can be repeated serially as necessary without accumulating radiation exposure. For physicians, the substitution of high-resolution ultrasonography eliminates the possibility of radiopaque media-induced allergy and hyperosmolar tissue damage from extravasation.

High-resolution ultrasonography can accurately evaluate abnormal adrenal glands, the renal parenchyma and collecting system, the ureters and the bladder. It is especially useful in children because of its superior ability to image hydronephrosis, accurately diagnose duplication anomalies and ureteral ectopia and evaluate renal parenchymal thickness and scarring. Ultrasonography is superior to conventional intravenous urography in evaluating hydronephrosis, which can be difficult to evaluate because of poor visualization due to decreased renal function from high-grade obstruction. These disorders are easily seen on ultrasonograms. Intrarenal masses and the abnormal parenchyma of renal dysplasia or cystic disease are also superiorly seen on ultrasonograms, as are renal duplications with nonfunctioning segments.

Ultrasonographic accuracy is limited by the resolution of the instrument and the diligence of the operator. Because of its superiority in imaging most pediatric urologic disorders and the fact that its use eliminates radiopaque media complications, radiation exposure and the traumatic milieu associated with invasive procedures, high-resolution ultrasonography has become the diagnostic procedure of choice for many of the problems seen in pediatric urology.

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Treating Female Urinary Incontinence

THE SUCCESSFUL ELIMINATION of female urinary incontinence requires that the cause be accurately identified because corrective treatment is specific to the origin. Patients who have urgency incontinence as the primary symptom, who do not have associated urethral or bladder neck hypermobility and who have bladder instability noted on a filling cystometrogram are most appropriately treated pharmacologically.

Patients with stress urinary incontinence in whom bladder pressures are stable during the filling cystometrogram and who have significant urethrovesical junction mobility will usually benefit from bladder neck suspension. This procedure can be done either through an abdominal or a vaginal approach. Success of the operation depends on adequate elevation and fixation of the urethra and bladder neck to their normal retropubic position.

If the procedure is done vaginally, the bladder neck is best elevated by placing large, monofilament, nonabsorbable sutures securely on the vaginal wall at each side of the urethrovesical junction, and, after pulling them up through the retropubic space from above, they are secured to the lower abdominal wall fascia or periosteum of the pubis and frequently then to each other.

Many urologists prefer to assure the appropriate placement of these sutures and the successful closing of the continence-providing portion of the urethra by inspecting the urethra cystoscopically as the sutures are tightened.

Those few (about 5%) who continue to have incontinence may achieve cure with another suspension (if the first failed to achieve anatomic correction) or they may be considered for a fascial sling procedure, artificial urinary sphincter or periurethral Teflon paste injection.

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The Health Policy Agenda for the American People

HEALTH CARE IN THIS NATION has become an enormously complicated affair. This is largely a direct result of the unprecedented advances in medical science and technology that have occurred, particularly over the past 40 years. The technologic result has been dramatic. Medical care in this nation is unsurpassed in what it can accomplish. The social, economic and political result has been a new kind of complex health care system that is unprecedented. Someone has said that it is kind of like a balloon—if you push it in one place it bulges somewhere else, and not much is changed. It has developed characteristics that seem to resist or defy such time-honored approaches as free enterprise, a free market or government regulation and control by laws. Each of these has been or is being tried but none seems to be working very well, if at all. For example, while the costs are perceived to be too high and uncontrolled, at the same time we are told that 40 million Americans have limited access to health care, and may not be receiving it, because they have no health insurance.

If free enterprise and government regulation do not seem to be solving the problems, then what might? Perhaps a different approach—such as collaboration among all the parties at interest—might be tried. With this in mind, in 1982 the American Medical Association began a formidable project to try to develop a "Health Policy Agenda for the American People." In 1987 the report of this project has become available. Over 425 representatives from 172 health, health-related, business, government and consumer groups participated. No other such study has ever included such a diverse group of participants. The goal was to decide on each position or recommendation by a consensus rather than just by a majority vote. The result of this process is indeed impressive. There are 195 recommendations. These deal with the supply of professionals, providing the technology and facilities, organizing the resources, communicating health information, ensuring quality, paying the bill and preparing for the future through research.

This was not only a massive process but, more importantly, it is also an innovative approach to understanding the complex, interdependent, technologic, social, economic, political system that health care has become and for trying to determine what needs to be done to make it work well. The problems are unprecedented—the system itself is unprecedented—and it is reasonable to expect that the solutions will also be unprecedented, and likely to be developed through an unprecedented approach. So much for the study. What happens next will be even more important. Will the 425 participants and the 172 organizations they represent really work as hard toward implementation of the recommendations that they all have agreed to by consensus? Will their efforts need to be coordinated in some way, again perhaps by some kind of agreement or consensus? Are 195 recommendations too much to tackle all at once or should there be some effort to set priorities?

The report, taken by itself, represents a monumental effort to deal with a monumental problem. Conceptually, the approach makes sense. If these kinds of problems are ever to be solved, the more there is consensus and the less there is coercion, the better. It seems reasonable that those in the study who made the recommendations and agreed to them would have an ongoing personal and organizational investment in seeing them carried out. If an interdependent system, such as health care now has become, is ever to run smoothly, then all its interdependent parts will need to run smoothly together. Too much competition within the system or too many rules imposed by parties outside the system do not seem to be the most appropriate way to have a smooth or even cost-efficient operation. There must be a better way. Perhaps the model used to develop these recommendations can somehow be adapted so as to help with their implementation.

Finally, one must acknowledge that it was leadership that brought the "Health Policy Agenda for the American People" into being, and it would seem that leadership will again be needed if its recommendations are ever to receive the consideration and action they deserve.

MSMW

Coma After Cardiac Arrest—How Much Care Is Enough?

UNTIL RECENTLY most victims of cardiac arrest died. The few who survived because of prompt reversal of the cardiac irregularity could often resume a normal life. In recent years, advances in medicine have resulted in increased success at reviving the heart, but the consequence is that many patients survive with a brain damaged by hypoxia-ischemia. As a result, most acute-care hospitals now care for a number of postarrest patients who survive in an unconscious state, and these patients also populate chronic-care hospitals, nursing homes, other health facilities and even private homes. This problem of brain damage after cardiac arrest is addressed by Longstreth elsewhere in this issue in a discussion of "The Neurologic Sequelae of Cardiac Arrest."

The American public has gained considerable sophistication about issues concerning irreversibly unconscious patients. In a recent poll published by the American Medical Association, 73% approved of "withdrawing life support systems, including food and water, from hopelessly ill or irreversibly comatose patients if they or their family request it."[1] The proportion of persons supporting this view did not differ significantly with respect to the age of the respondent. Courts are also beginning to address issues raised by irreversible unconsciousness. In addition to the cases cited by Longstreth are the recent cases of Brophy[2] and Jobes.[3]

In general, serious decisions about continued care for an unconscious person belong to the affected patient (while sentient) and his or her family, but to make these decisions requires that they be informed about the "hopelessness" or "irreversibility" of unconsciousness. Until recently, there was very little published information that would aid physicians in evaluating prognosis. Longstreth and his collaborators are one of the groups that have made important contributions, and his discussion nicely summarizes his published reports.

As he notes, easily evaluated clinical variables such as the pupillary reaction to light, spontaneous eye movements and the motor response to command or pain have been found to identify subgroups of patients with relatively good or poor

chances of recovery. When a score for glucose level at admission was added to scores for these three clinical variables, Longstreth was able to identify groups with chances of awakening that ranged from 0% to 95%. Because of missing data, summed scores were possible in only 315 of 389 patients (81%),[4] and patient numbers at the two extremes were only 14 for a score of 0 and 22 for a score of 9. These problems of missing information and cutting the population too fine, however, confound most such prediction efforts.

In our study of recovery from coma caused by cardiac arrest,[5] we identified the same clinical variables as the most important discriminators early after an arrest. Overall, 22% of our 210 postarrest comatose patients ever regained full consciousness, and only 12% recovered enough to live independently. Of our 210 patients, 52 lacked the pupillary light reflex, and none of them ever regained the ability to lead an independent life. By contrast, 27 patients had preserved pupillary reflexes, some motor response to pain and spontaneous eye movements that were roving conjugate or better; 41% (11) of this group regained independent function.

Readers should note several differences among these and other[6-12] studies of recovery from coma, differences that matter if the prediction instruments are to be used clinically. One relates to the dependent variable. Longstreth and coworkers used awakening, by which they meant recovery of consciousness, with demonstrated ability to speak comprehensibly and follow commands. (Unlike Longstreth, we would consider a vegetative patient[13] to have awakened, in that the eyes are open, and the patient appears awake, even while failing to display learned behavior or behavior demonstrating awareness of the environment.) Our outcome variable, by contrast, was related to function, the ability to live independently or to return to the premorbid level of existence. Clinicians must choose studies that define outcome variables most consistent with the stated views of their patients.

Another difference among studies relates to the nature of the predictive instrument. For Longstreth, as for Jennett and collaborators,[12] an aggregate score was selected, in part because of ease of use. By contrast, we decided to represent our predictions in the form of a decision tree. With aggregate scores, a user should realize that there are different ways to achieve the same score. For example, a score of 3 could be achieved by Longstreth with more than ten different combinations of the four subscales. There is no a priori reason to believe that all of these combinations are equivalent in terms of predictive power or that a motor score of 4 is twice as "good" as a score of 2 on the same subscale. Even though these aggregate scores often relate well to outcome and may be easy to use, inevitably information is lost when nonequivalent scores are summed.

A final important difference, noted by Longstreth and elsewhere by me,[14] relates to the measure by which a predictive scheme is to be assessed. For many, that measure is simple accuracy. When dealing with issues of the level of care for comatose patients, many would argue that some prediction errors are more serious than others. Prediction instruments can be adjusted either to minimize all errors equally (and thus maximize accuracy) or alternatively to minimize some errors at the expense of others. Longstreth, Diehr and Inui noted the seriousness of "mistakenly predicting that a patient would never awaken."[4] We concur because we fear that care might be withdrawn from a patient possessing the potential for good recovery. Another way to view this problem is to consider that the prediction instrument is designed to identify patients who will do poorly. Taken this way, specificity (not making the false-positive error of predicting poor outcome in someone who does well) is more important than sensitivity (not predicting poor outcome in everyone who does badly).

Longstreth draws attention to the importance of blood glucose levels for outcome after cardiac arrest. As he notes, there is ample experimental evidence to support this observation, although in clinical material, one cannot be certain that the "admission" glucose reflects the glucose level at the time of ischemia or whether it reflects reactive hyperglycemia or even intensity of intravenous management and thus severity of the arrest. That blood glucose might influence focal ischemia (stroke) as well as global ischemia (cardiac arrest) is suggested retrospectively[15] and prospectively[16] by observations that even modest elevations in blood glucose (above 120 mg per dl) are associated with a poor outcome after stroke.

How are these prediction methods to be used? The first question is whether they should be used at all. Longstreth notes that none of these techniques have yet been tested prospectively, and thus their applicability to new patient populations remains questionable. All current prediction instruments, however, are predicated on judging the likelihood of neurological recovery, and by so doing, they are likely to be preferable to current practice in some situations.

In 1981 Chipman, Adelman and Sexton[17] distributed a questionnaire to physicians in the Portland, Oregon, area regarding circumstances under which cardiopulmonary resuscitation (CPR) would be discontinued. Patient age over 65 would be sufficient grounds to discontinue CPR for 4% of the respondents, and age over 75 would lead to discontinuation of CPR for 9%. If the patient had been transferred from a nursing home, 18% of respondents would cease CPR. Cardiac arrest resulting from massive head injury would lead 44% to discontinue CPR; arrest in a patient with severe mental impairment would result in cessation of CPR by 54%, and the coexistence of end-stage disease would lead 87% to stop CPR. The lack of unanimity in response emphasizes the different thresholds physicians place on the value of continued resuscitative efforts. Many, however, will find simple criteria of age (65 or 75) to be too simplistic. Assessment of prognosis based on the likelihood of brain recovery seems more realistic than many of these criteria.

The issue is that decisions about care for the unconscious are made now, often on the basis of imperfect criteria like age. Efforts such as Longstreth's that improve the validity of criteria for continued care of the unconscious will help matters, so long as their limitations are known and the ultimate decision is left to the individual physician, patient and family.

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The Battlefield Called Sarcoidosis

SARCOIDOSIS HAS BEEN with us for 100 years or so; in Jonathan Hutchinson's day, it was a dermatologic curiosity. In the twilight of his life, radiography was introduced and sarcoidosis was recognized in lungs and bone, thereby making it a multisystem disorder. During this century every new technique has provided a fresh approach and added new dimensions. The chest physicians, dermatologists and ophthalmologists have been joined by the gastroenterologists, epidemiologists, geneticists and immunologists. All these disciplines come together for a World Congress on Sarcoidosis every three years. That is why every congress and its transactions maintain high levels of academic interest and even spawned a new *Journal of Sarcoidosis and Other Granulomatous Disorders*. In medicine, and in many other human pursuits, the obscure tends to fascinate, and this explains in part the deep interest that internists have long maintained in sarcoidosis.[1]

New techniques introduced to medicine have provided exciting new dimensions of sarcoidosis. Fluorescein angiography displays with clarity the retinal vasculitis of sarcoid uveitis.[2] The leakage of dye is, of course, an indication for steroid therapy to prevent blindness. Computed tomographic scanning is an excellent technique for identifying mediastinal masses and defining sarcoid lymphadenopathy and for recognizing hydrocephalus and space-occupying cerebral sarcoidosis. Magnetic resonance also displays basal sarcoid meningitis and involvement of the bundle of His by myocardial sarcoidosis.

The sarcoid granuloma is a battlefield between invading antigens or irritants and the cellular and humoral defenses of the body. New techniques including immunofluorescence, histochemistry, monoclonal antibodies and the enzyme-linked immunosorbent assay (ELISA) have provided new insights in this immunologic battlefield, for it is now possible to identify the uniforms of the participating warriors. One of the principal gladiators is the activated helper Leu 3^+ DR^+ T-lymphocyte releasing interleukin-2 in abundance. Although the initiating signal for this exaggerated T-helper/inducer lymphocyte inflammatory response is not yet recognized, it seems that local stimuli in the battlefield maintain this exaggerated state of alert. The activation of the interleukin-2 gene is compartmentalized, for lung T cells express interleukin-2 messenger RNA transcripts, whereas peripheral blood T cells do not have this property. This expression of the interleukin-2 gene is suppressed when lung T cells are placed in culture.[3] Levels of soluble interleukin-2 receptors measured by an ELISA technique are elevated in serum and bronchoalveolar lavage fluid in active sarcoidosis.[4]

What is the provocateur of this warfare? Many initiating signals have been claimed but none have been implicated in a reproducible manner. Van Gundy and Sharma have reviewed all claims made in the past 30 years. This update—or should it be termed a pause for reflection?—will repay study by any investigator tackling one of the remaining riddles of the sphinx, namely, the etiology of sarcoidosis. They consider and reject *Mycobacterium tuberculosis*, phage-infected lysogenic mycobacteria, mycoplasma, fungi or a viral cause. Neither are they able to substantiate claims for hair spray, peanut dust, beryllium, clay-eating, zirconium, mineral oil, talc powder, phenylbutazone or smoking.

Sarcoidosis has many features in common with autoimmune disorders, including similar clinical and immunologic patterns, predisposing human leukocyte antigen (HLA) types and even similar responses to treatment.[5] They both share such clinical manifestations as uveitis, erythema nodosum, thyroiditis, Addison's disease and Sjögren's syndrome, for which Sharma has neatly devised the acronym "TASS syndrome."[6] Sarcoidosis is sometimes recognized in association with primary biliary cirrhosis, Crohn's regional enteritis and celiac disease, posing the query whether there is a causal relationship or whether it is coincidental. If the relationship can be established as causal, then the enigma of pathogenesis is nearer a solution. If the relation is a coincidental overlap, then it may produce confusion rather than clarity. The link between sarcoidosis and Crohn's regional enteritis has momentarily been strengthened by two French studies that show that patients with Crohn's disease have latent pulmonary involvement.[7,8] They noted bronchoalveolar lavage lymphocytosis similar to that observed in sarcoidosis, an increased physiologic dead space in the upper parts of the lung and increased superoxide anion production by alveolar macrophages. There were also significant differences, however, for patients with Crohn's disease had significantly lower serum angiotensin-converting enzyme levels and there was no mediastinopulmonary gallium 67 uptake in these patients. The vital missing link in the conjecture that sarcoidosis is an autoimmune disorder is the failure to recognize specific circulating sarcoid autoantibodies apart from a single unconfirmed Swiss report.[9]

The Van Gundy-Sharma review also raises the possibility of a genetic or environmental predisposition, or what is sometimes regarded as a sarcoid terrain. Irish women in London and Puerto Ricans in New York are prone to erythema nodosum. Hormonal factors play some part, for erythema nodosum due to sarcoidosis is commoner during the childbearing years, during early pregnancy and also in women taking oral contraceptives. Sarcoid arthritis and erythema nodosum are most likely to occur in patients who are HLA-B8, -A1, -Cw7 and -DR3. Patients with chronic (as compared with acute) sarcoidosis are more likely to be HLA-B13. The occasional occurrence of familial sarcoidosis suggests a racial predisposition with a recessive mode of inheritance for susceptibility.[1]

The pathogenesis of sarcoidosis seems multifactorial, so investigators in many different disciplines will next meet to

provide new insights, apply novel techniques and unfold fresh theories at the Eleventh World Congress of Sarcoidosis and other Granulomatous Disorders, to be held in September 1987 in Milan, Italy.

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Sexual History-Taking

THE INCURABILITY and rapidly increasing fatality rate of the acquired immunodeficiency syndrome (AIDS) have aroused in the medical and health professions a concern about preventive measures that rivals the attention we have for years been giving to the prevention of heart disease and cancer. While researchers focus on possible origins and cures, the immediate challenge for practicing physicians is to determine which patients are at risk of contracting or spreading AIDS. As Lewis and Freeman discuss elsewhere in this issue, we already know that sexual life-style is one of the leading AIDS risk factors, and, therefore, it is necessary to ask patients about their life-styles as part of a comprehensive health care evaluation. But talking about sex, or sexual life-styles, presents a different sort of challenge than talking about diet, smoking or exercise, risk factors for other common diseases.

Lewis and Freeman point out that physicians, because of personal discomfort, have difficulty discussing sex with patients who may have same-sex partners. Ample literature indicates there is a wide variety of sex-related topics that are difficult for physicians to discuss. Talking about sex with elderly patients, or severely disabled patients, or discussing extramarital or premarital sex, may arouse discomfort and avoidance. Numerous studies have been done to determine the best teaching methods to improve comfort and knowledge levels through medical school and continuing education courses on human sexuality.[1,2]

Unfortunately, similar studies have not been done on how to best put to clinical use sexuality comfort and knowledge. Many questions remain in regard to how to best incorporate a sexual history into routine medical history-taking. What is the difference between taking a sexual history in a psychiatric setting and in a general medicine practice, and where are the scientific studies of the effectiveness of one type of sexual history-taking versus another in eliciting medically useful information or information of therapeutic value in a nonpsychiatric setting?

Various approaches to sexual history-taking by physicians have been recommended in textbooks and articles.[3-5] Two of the more obvious areas of conflicting recommendations have to do with how to initiate the discussion of sexual function, and the minimum of questions that should be asked of patients during history-taking in nonemergency situations. Green suggests initiating sex-related questions with a variation of:

> One area of health which has been relatively neglected by physicians in the past is sexual health. It has become increasingly apparent that if we are to fulfill all our responsibilities to patients this important part of our lives must also receive attention. Therefore, I am going to ask you a number of questions about sexuality. . .[6]

Using such qualifiers as openers is refuted by others who suggest eliminating opening rationales and asking directly about sexual function, getting the sexual physiology particulars when other physiologic questions are being asked during a routine review of systems.[7,8] A few direct questions during a review of systems might be the more efficient and effective way of introducing the topic of sex and determining if there are any risk factors or problem areas that warrant further exploration. Reich states that patients appreciate direct questions (not "how is your sex life?") and that screening questions should be routine. "Otherwise, the physician may overlook problems, may return to the subject as an afterthought, or may experience tension or show embarrassment when trying to think of a screening question during the history."[8]

When asking questions about the genitourinary system, it is logical to ask women about vaginal pain and men about erectile function. Such direct functional questions pave the way to questions about sexual activity: frequency, partners, satisfaction. A direct manner of asking about sexual activity invites a direct response, such as "Do you have more than one sexual partner? Is (Are) your partner(s) male or female (or both)?" We must not assume people are monogamous or heterosexual just because they are married. We must not assume they are celibate if they are single, elderly, disabled or in some way could be considered unattractive.

When a physician shows a willingness to talk about physiologic specifics and alternative life-styles, the patient is prepared to respond frankly to follow-up questions such as "How has your present illness (disability) affected your sexual functioning or relationships?" and "Do you have any concerns about your sexual functioning?" This method of going from specific questions to general ones is contrary to the usual sequence in history-taking, but may be a good way to invite a frank response to the general questions. When the general questions and questions about sexual satisfaction and behavior are asked first, the patient is not sure how specifically or openly to respond.

Munjack and Oziel clearly distinguish between a screening history and a problem-oriented history.[9] Others recommend a single detailed history-taking that includes questions about sex education, masturbation practices, sexual fantasies and a wide variety of questions that may not be practical for inserting in the routine history-taking format of most general medical evaluations. Singling out the sexual area of a patient's history for a 20-minute review may turn away patients who do not understand the relevance of such detail unless they have expressed a sexual concern. Obviously, once a concern is expressed, further exploration is necessary for proper diagnosis, treatment or referral.

Both physician and patient must accept the relevance of the sex-related questions if the physician-patient relationship is to be maintained or enhanced by such frank discussion and

if medically essential information is going to be elicited. Using a brief screening history, followed by a problem-oriented history when indicated, physicians in one study found that asking patients about their sexual functioning was of medical value in 50% of cases. In this study, 98% of the patients who had been asked about sexual function reported that this questioning was appropriate.[10] The study predated the AIDS epidemic.

Medical value and appropriateness were reported when the issues raised by sexual history-taking had more to do with the quality of life than the threat of loss of life. While AIDS may be an important impetus to begin including sexual histories in medical history-taking, it would be unfortunate if the sexual history is only valued for its ability to disclose risk for a life-threatening disease. When sexual problems go unrecognized, they may become the basis for nonsexual presenting complaints such as insomnia, headaches, backaches, depression or vague somatic complaints. Literature on sexuality and cancer, renal disease, spinal cord injury and countless other diseases or disabilities emphasizes that attention to sexual concerns and dysfunctions can have a positive impact on physical and emotional well-being.

Through sexual history-taking physicians can determine if sexual problems are the result of the use of drugs or alcohol, the presence of vascular or neurologic disease or other diseases or disabilities, the treatment of which might alleviate the sexual problems. Each year with persistent exploration of problems in sexual function, research increases our understanding of the interconnection between sexual function and other aspects of the physiologic system. Whereas ten years ago most sexual problems were considered psychological problems, today we have discovered the adverse impact of vascular disease on erectile function, radiation treatment on libido, drugs on libido and erectile function and many other areas in which sexual problems prove to be medical in origin. Improved routine sexual history-taking is likely to suggest more answers to the questions that remain for sexual problems that do not improve with psychiatric treatment.

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Are We a Violent Nation?

THERE HAS BEEN violence in this world for a long time, probably since long before recorded history. We like to think of ourselves as a peaceful nation. Certainly we yearn for peace, even while we are upgrading our national armaments as a deterrent against needing to use them. Even so, we found ourselves in four major armed conflicts in the name of peace during the present century. There surely was violence in these conflicts, but this violence was deemed necessary, and, in the context of the times, even unavoidable. But does this mean that we are really not a violent nation? By one means or another we seem to have acquired most of what we need, and as a nation we have no reason for aggression or to use violence to achieve expansionist goals. In fact quite the contrary—we would like nothing more than to live in a world genuinely at peace. Some other nations are less fortunate, and some are aggressive and may even resort to violence in an effort to achieve their perceived goals. So it seems certain that there will continue to be violence in the world in which we live.

But when we look at ourselves internally there is considerable evidence that many Americans really must enjoy violence for whatever reason. One needs only to watch the newscasts on television, read the newspapers, scan the offerings at the movies (particularly the violent and horror movies so enjoyed by young people), to sense that the public at large must have more than a casual interest in violence, not to mention crime. Even the "Star Spangled Banner," the national anthem, has its "bombs bursting in air," while the more peaceful "America the Beautiful" has never achieved status as our national anthem.

One can only wonder if there is a difference between what we say we are—a peace-loving people—and the aggressive, competitive people we seem to be, also a people that somehow enjoys or seems to get some satisfaction—vicarious or otherwise—out of violence. One can only guess at what effect all this imagery of violence has on our people, especially the young people. When one sees small boys gleefully shooting at passing automobiles (or at each other) with toy hand guns, one can only wonder where they got the idea. And their parents may very likely have given them the toy guns and, if so, where did they themselves get the idea? It is hard to believe that such things do not reflect a tacit acceptance of violence as a more or less integral part of the life of this nation and a tacit acceptance of a special interest in violence by the media.

Americans must remain an aggressive and competitive people if they are to hold their own in this modern world. They must learn how to be aggressive and competitive in an aggressive and competitive world, and many of them must learn this through the imagery of the news media. But must we accept or condone the exploitation of violence that we see all about us, recognizing that this very exploitation can lead to further violence that can then be exploited?

Physicians are familiar with the aftermath of violence. They try to repair the injuries, whether physical or emotional or both. They know the cost in dollars and human misery. Perhaps it is time for the medical profession to be more active in the prevention of violence, if not aggressiveness. True, the profession has already spoken out against violence, perhaps even with some effect. But the imagery not only persists, it is thriving. Physicians are respected when they speak with authority on matters of illness and injury. Perhaps it is time to document the correlation between violent imagery and violent action, and then to speak and act even more forthrightly in the interests of patients, the public in this matter, as we proceed in our quest for a healthier nation.

MSMW

Case Reports

Diabetic Lipemia With Fatty Splenomegaly Culminating in Unnecessary Splenectomy

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ELECTIVE SPLENECTOMY is usually undertaken for staging lymphomas, treating cytopenia or for mechanical reasons. Occasionally splenectomy is needed for the diagnosis of splenomegaly of obscure cause.[1]

A patient presenting with uncontrolled diabetes mellitus, lipemia and splenomegaly in the absence of abdominal pain underwent a diagnostic splenectomy. Preoperatively, an unusual feature of hyperlipoproteinemic splenomegaly—low-grade hemolysis—was present. In retrospect, fatty infiltration should have been considered as the cause of persistent splenomegaly. It is rational to observe such patients during effective lipid-lowering therapy before a diagnostic splenectomy is undertaken.

Report of a Case

The patient, a 58-year-old man, had a 13-year history of neglected non-insulin-dependent diabetes mellitus with sensory neuropathy and erectile dysfunction. He also had long-standing essential hypertension, hypertriglyceridemia, gout and obesity. He followed no diet, took 40 units of isophane (NPH) insulin and 20 units of crystalline zinc insulin in a single daily injection and was receiving clonidine, triamterene, hydrochlorothiazide, indapamide and allopurinol. Six months earlier a regimen of probucol, 500 mg twice a day, was begun "to lower cholesterol." One sister, aged 86, was reported to have diabetes, gout and hypertriglyceridemia. Another sister died of myocardial infarction at age 58.

Background diabetic retinopathy was present; lipemia retinalis, xanthomatosis and hepatomegaly were not observed. The spleen was palpable 6 to 8 cm below the left costal margin. Touch sensation was diminished over the feet and ankles.

Laboratory studies elicited the following values: serum sodium was 126, potassium 3.9, chloride 91 and bicarbonate 26 mEq per liter; glucose was 450, urea nitrogen 30, creatinine 1.7 and uric acid 10.2 mg per dl. Serum levels of aminotransferases, bilirubin and alkaline phosphatase were all normal. A fasting plasma cholesterol was 292 and triglycerides were 7,728 mg per dl. The plasma was not examined for chylomicronemia.

A blood leukocyte count was 3.7 to $5.0 \cdot 10^3$ per μl, platelets 1.2 to $1.3 \cdot 10^5$ per μl and packed red cell volume 47%. A modest reticulocytosis (3.9% to 4.8%) was seen (Figure 1). Occasional spherocytes were observed in the peripheral blood smear. Coombs' and osmotic fragility tests and a serum protein electrophoresis were normal. A specimen of bone marrow showed a normal number of megakaryocytes with erythroid hyperplasia and vacuolated reticuloendothelial cells (Figure 2).

After two weeks of a regimen of twice-a-day insulin (NPH and regular insulin, 30 and 15 units in the morning and 14 and 10 units in the evening, respectively) and a 2,000-kcal American Diabetes Association diet, the plasma cholesterol level was 223 mg per dl and triglycerides 690 mg per dl. Chylomicronemia was absent. Ultracentrifugation and electrophoresis of a plasma specimen taken with the patient in a fasting state showed elevated very-low-density-lipoprotein levels with greatly decreased levels of low- and high-density lipoproteins (type IV hyperlipoproteinemia).

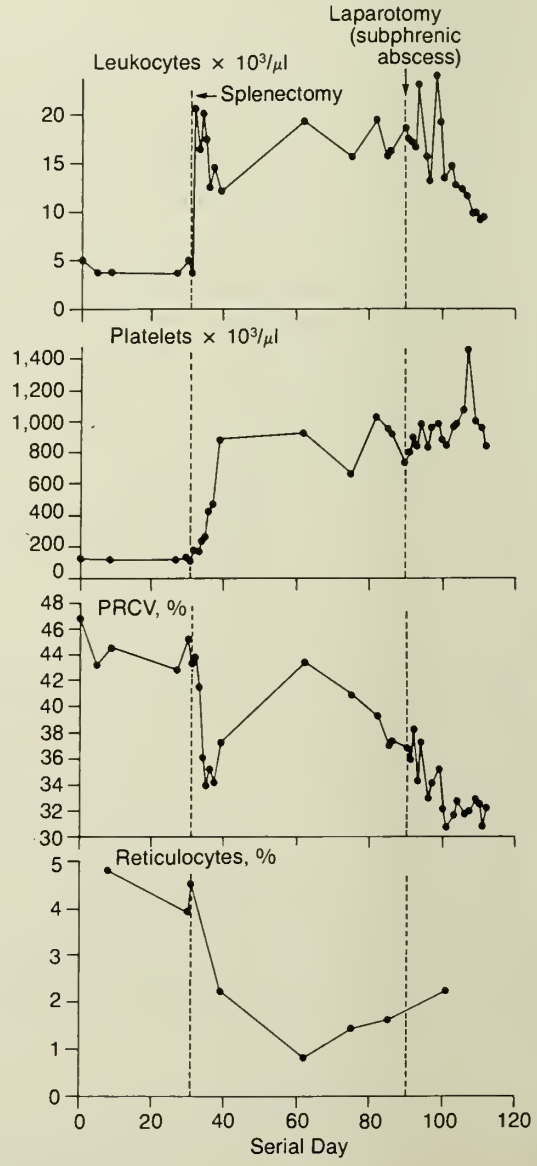

Figure 1.—The graphs show the clinical course of the patient before and after a splenectomy. PRCV = packed red cell volume

(Small JM, Moatamed F, Deiss A, et al: Diabetic lipemia with fatty splenomegaly culminating in unnecessary splenectomy. West J Med 1987 Aug; 147:196-198)

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At laparotomy four weeks after admission, the spleen weighed 850 grams. Hematoxylin and eosin-stained sections showed foamy histiocytes that stained positively with Sudan black and oil red O. Electron micrographs showed vacuolated foam cells (Figure 3). No lamellated or tubular bodies or ceroid was seen.

Reticulocyte counts fell to 0.8% to 2.2% in the postoperative period (Figure 1). Seven weeks after discharge, the patient presented with fever, chills and weight loss. A left subphrenic abscess was drained. Moderate hypertriglyceridemia (300 to 628 mg per dl) with decreased high-density-lipoprotein cholesterol (32.5 mg per dl) persisted. Two years after splenectomy, hematologic indices were normal, hemoglobin A_{1C} was 6.3% and there was a draining sinus in the splenectomy scar.

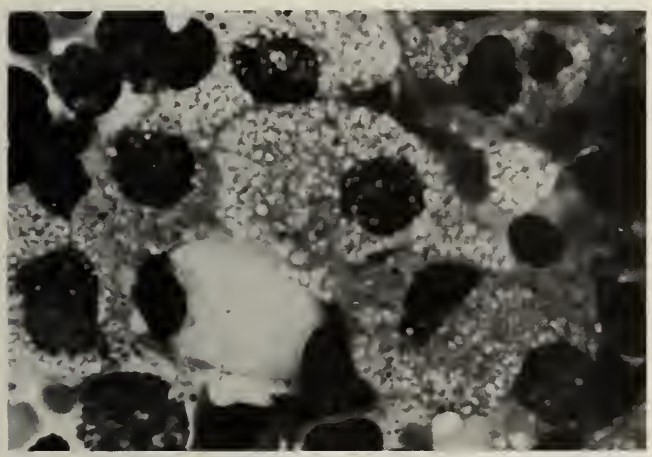

Figure 2.—Histologic examination of a bone marrow specimen (Giemsa stain) shows vacuolated reticuloendothelial cells (original magnification × 1,000).

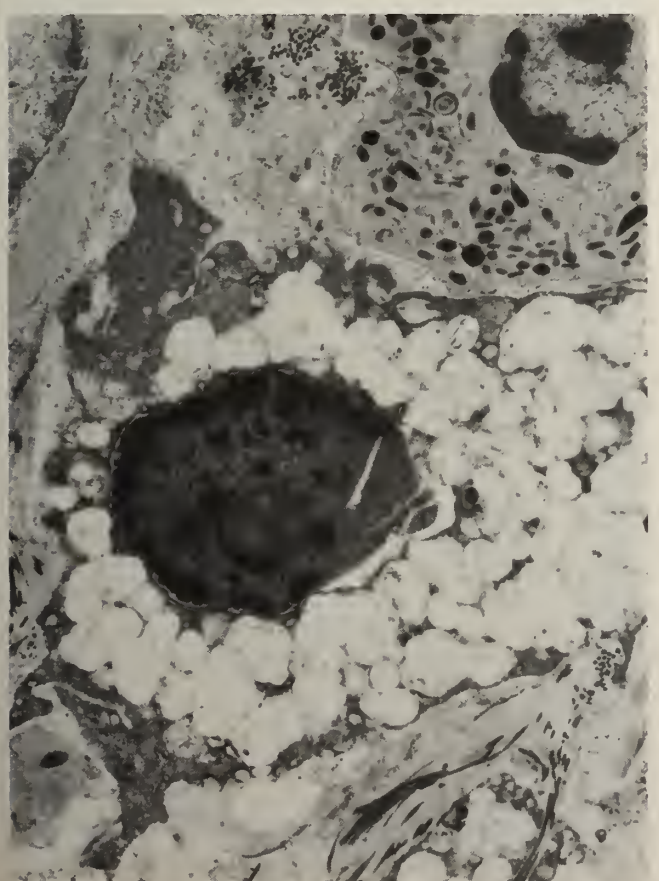

Figure 3.—Electron microscopy of a specimen of spleen shows macrophages with numerous vacuoles containing granular material staining less densely than neutral fat (original magnification × 4,000).

Discussion

Hyperlipoproteinemia with hypertriglyceridemia and chylomicronemia (types I and V) is a recognized cause of hepatosplenomegaly,[2,3] yet standard textbooks usually fail to include it among the causes of splenomegaly. In this patient, splenomegaly was not associated with an abdominal pain crisis, the clinical context in which it has most often been reported.[2] It is likely that chylomicronemia was present initially when the fasting triglyceride concentration exceeded 7,000 mg per dl, but the severe hypertriglyceridemia remitted promptly during treatment, diverting attention from lipemia as a cause of splenomegaly. Thus, when lipoprotein analysis was done two weeks after admission, the patient showed type IV hyperlipoproteinemia.

The significance of vacuolated reticuloendothelial cells in the bone marrow aspirate was not appreciated preoperatively; the correct diagnosis became clear only after foamy macrophages were noted on histologic examination of the spleen. In retrospect, a splenectomy and its resulting complications might have been avoided.

Diabetic lipemia, of which this patient had typical features, occurs when uncontrolled diabetes and an inherited disorder of lipoprotein metabolism coexist.[4] The patient had also received several drugs known to increase plasma triglyceride concentrations.[5] He probably had had long-standing chylomicronemia at the time of presentation. With severe chylomicronemia, the spleen, liver and bone marrow accumulate macrophage-derived foam cells engorged with lipid droplets and ceroid.[6]

Fatty splenomegaly was associated with hematologic abnormalities. Reticulocytosis in the absence of blood loss along with erythroid hyperplasia of the bone marrow and low-normal leukocyte and platelet counts was consistent with splenic sequestration of the cellular elements of blood. Blood loss and subphrenic abscess with inflammation undoubtedly contributed to postoperative anemia.

Successful treatment of diabetic hypertriglyceridemia requires control of hyperglycemia, reduction of excessive body weight and drug therapy in selected patients.[7] The use of probucol was inappropriate in the present case because it is ineffective for treating hypertriglyceridemia and often reduces plasma high-density-lipoprotein concentrations.[8] Furthermore, there is evidence from experiments in rabbits that probucol diverts lipoproteins from their normal catabolism through the low-density-lipoprotein (apoB,E) receptor to non-receptor-mediated catabolic pathways.[9] Thus, it is possible that administering probucol contributed to reticuloendothelial lipid deposition in this patient.

Correction of severe hypertriglyceridemia usually results in a reduction in the size of an enlarged fatty spleen. Patients with severe hypertriglyceridemia and otherwise unexplained splenomegaly deserve observation during effective lipid-lowering treatment before a diagnostic splenectomy is undertaken.

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Tuberculoma of the Brain Stem

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In North America, tuberculosis rarely involves the central nervous system (CNS). In developing countries, CNS manifestations of tuberculosis are more common. Patients may present with tuberculous meningitis, tuberculoma, tuberculous abscess and Pott's disease.[1] Tuberculomas are thought to occur most frequently in children.[1,2] Although potentially curable, tuberculomas often present a diagnostic puzzle, and the diagnosis may not be considered early in a patient's course. When a tuberculoma occurs in the brain stem, early diagnosis is critical if the patient is to survive. In Europe the incidence of intracranial tuberculoma may be increasing, partly because of an increasing number of refugees from developing countries.[2] The increasing inflow of refugees into the southwestern United States compels us to alert US physicians to this rare but curable lesion.

Report of a Case

At the time of presentation, the patient, a 70-year-old right-handed Cambodian woman, complained of slowly progressive nausea, vomiting, unsteady gait and double vision over three months. She had lost 9 kg (20 lb); a purified protein-derivative (PPD) skin test was reportedly positive in the past. She had no history of a transient ischemic attack, stroke, seizure or known cancer. She had lived in San Diego four years, having moved from Cambodia. She was taking no medications other than prochlorperazine for nausea. The patient was cachectic but there were no other findings on general medical and gynecologic examinations. On examination through an interpreter, her mental state was normal. On the left, there was a mild sixth nerve paresis and a mild lower motor neuron-type facial paresis. The other cranial nerves were normal. On motor testing, the right upper and lower extremities were mildly weak. Appreciation of pin, touch, vibration and position was moderately diminished in the right upper extremity and slightly diminished in the right lower extremity. Reflexes were present and symmetric with downgoing toes. There was an intention tremor in the right arm and leg. The patient was unable to stand because of ataxia; on sitting there was truncal titubation.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
ESR = erythrocyte sedimentation rate
PPD = purified protein derivative

The patient was admitted to the hospital for a presumed left pontine mass lesion and the following studies elicited no abnormalities: complete blood count, electrolytes, calcium, liver function tests, thyroid function tests, serum B_{12} level, coagulation studies, urinalysis, arterial blood gas determinations, intravenous pyelogram, liver-spleen scan and abdominal ultrasonogram. A bone scan was abnormal at the site of an old trauma in three ribs on the right. An erythrocyte sedimentation rate (ESR) was 47 mm per hour. Skin tests were negative for PPD and positive for mumps and *Candida*. A computed tomographic (CT) head scan with and without contrast infusion showed a round enhancing lesion in the pons, with mass effect and surrounding edema (Figure 1). A lumbar puncture produced a clear colorless fluid under normal pressure with a glucose concentration of 46 mg per dl (concurrent serum glucose level, 98 mg per dl), protein 41 mg per dl, 2 lymphocytes and 1 erythrocyte per μl. Smears and cultures for fungi, bacteria, acid-fast bacilli and cytologic examination were normal. Bone marrow aspiration failed to produce acid-fast bacilli on smears and cultures. A cerebral angiogram confirmed the presence of an avascular mass in the pons.

Treatment with dexamethasone, isoniazid, rifampin, ethambutol hydrochloride and pyridoxine hydrochloride was begun. After two weeks the patient's condition had improved to the point that she was no longer vomiting, could ambulate with no assistance and showed nearly normal strength on the right. Her left sixth nerve paresis and diplopia persisted. Over the ensuing months she continued to show slow improvement, and after 18 months the antitubercular therapy was stopped; the dexamethasone dosage was tapered 20 months after presentation. When last examined, the patient continued to have a subjective loss of appreciation of pin and touch in the right arm. There were no objective sensory, motor, reflex, cranial nerve or cerebellar findings. Follow-up CT scans showed resolution of the mass and persistence of a small lucency in the pontine tegmentum.

Comment

The clinical findings in the patient presented herein clearly suggested a lesion in the left pons. The history of slowly progressive symptoms over months suggested a mass lesion. The CT scan confirmed the location of the lesion, and the enhancement pattern suggested hypervascularity or blood-brain-barrier breakdown. The mass was shown to be avascular on angiography. Thus, the lesion was a solitary, round, avascular mass with significant blood-brain-barrier breakdown. The cerebrospinal fluid (CSF) findings essentially ruled out bacterial or parasitic abscess, as did the absence of fever or serum leukocytosis. A primary malignant tumor was searched for but not found. The patient was treated for tuberculous granuloma, and the successful resolution of the lesion eliminated metastasis, fungal abscess and other granulomatous disease as possibilities.

(Lyden PD: Tuberculoma of the brain stem. West J Med 1987 Aug; 147:198-200)

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This work was supported in part by a Career Development Award from the Veterans Administration.

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The incidence of CNS tuberculoma ranges from 0.15% of intracranial tumors in Britain[3,4] to 20% to 30% in India.[5] In the United States, 16% of Cushing's series of brain tumors were tuberculomas.[6] Sibley and O'Brien found an incidence of 0.7%.[7] Recent studies in England have documented a higher incidence or at least greater recognition of intracranial tuberculoma.[2,8] The authors emphasized the changing incidence of the disease, perhaps reflecting an increase in immigration from India, Africa and Southeast Asia.

The diagnosis of intracranial tuberculoma should be considered in any patient from a developing country, or with other appropriate exposure, in whom signs and symptoms of a slowly growing cerebral mass develop. Most patients present with weight loss and a positive PPD skin test, and about half will show no evidence of extracranial infection.[2,3,5,8,9]

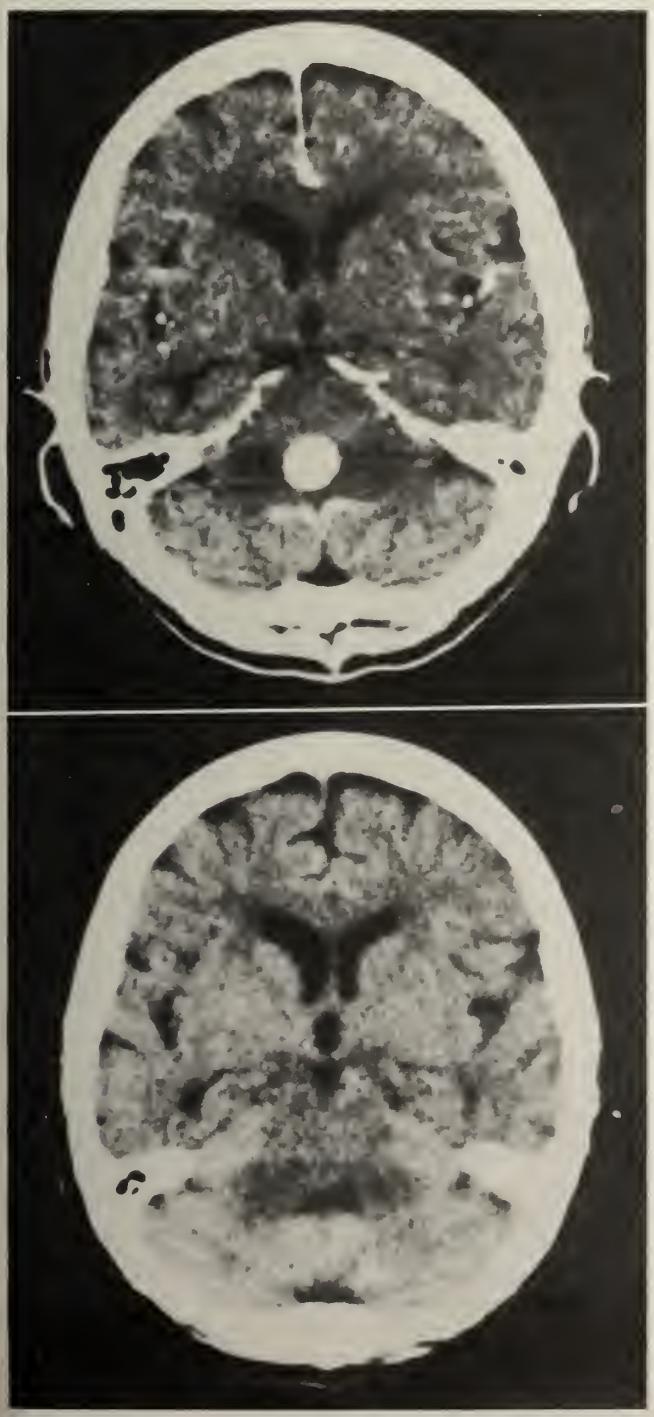

Figure 1.—Initial computed tomographic head scans are shown with (**top**) and without (**bottom**) contrast. Note a round, homogeneously enhancing lesion in the pons without appreciable surrounding edema. The level shown is at the midpons.

Examination of a specimen of the CSF from a patient with infratentorial tuberculoma may show no abnormalities or may show evidence of infection.[9-14] CSF protein can be normal, but more typically is elevated. Cultures and stains for acid-fast bacilli do not appear to be useful. Although the ESR is usually elevated, it can be normal. The case reported here illustrates that a high index of suspicion is required to make the correct diagnosis.

Supratentorial masses are said to occur more frequently in adults and infratentorial masses more frequently in children, but, as in this case, the lesion can appear in any location.[2-4] Infratentorial lesions in adults have been reported previously, and the reports emphasize unusual symptoms such as facial myokymia, tic douloureux and waxing and waning symptoms mimicking arteriovenous malformation.[9-14] Our patient is exceptional for her age, as brain-stem tuberculoma has not been previously reported in the elderly. The most useful test in confirming the diagnosis of intracranial tuberculoma is the CT scan.[12-18] Tuberculomas are typically solitary, round and enhance homogeneously with contrast infusion.[15] Surrounding edema is minimal and rarely do the lesions enhance as a ring.[11-14]

There are no definitive guidelines for therapy for brain-stem tuberculoma. Patients treated with surgical excision plus antitubercular chemotherapy or with medical treatment only have done well.[10-14] Other authors have reported deaths in patients treated only medically, but in those cases treatment was begun too late to have influenced the outcome. The patient presented here received three antitubercular drugs until the enhancement on contrasted CT scan completely resolved, and there has been no recurrence. The prognosis in brain-stem tuberculoma depends on the timing of diagnosis. The reported deaths have occurred in patients with multiple lesions involving the cerebellum and brain-stem who were diagnosed late in their course.[9,11] In the reported cases where medical or surgical therapy (or both) was begun early, all patients survived.

In conclusion, brain-stem tuberculoma should be looked for in any patient with a history of exposure, particularly in refugees from Southeast Asia. Treatment will produce an excellent outcome; without early treatment, patients will die. Laboratory studies, including ESR, PPD and CSF studies, can be normal. Alert physicians should initiate therapy based on suggestive findings on the history, examination and CT scan and should not be deterred by a lack of microbiologic confirmation.

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Pasteurella multocida Urinary Tract Infection

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PASTEURELLA MULTOCIDA is a small, gram-negative bacillus most commonly recognized as a cause of soft tissue infection in animal bites and scratches.[1] *P multocida* urinary tract infections are rare and all reported cases have occurred in debilitated patients.[2] To our knowledge, this is the first reported case of *P multocida* causing a symptomatic urinary tract infection in an otherwise healthy woman.

Report of a Case

The patient, a 31-year-old woman, was admitted for fever, flank pain and bacteriuria. Except for a 20-pack-year smoking history, she was in good health. Ten years earlier she presumably had a left pyelonephritis.

Three weeks before admission right flank pain developed without dysuria, hematuria or other urologic symptoms. She had no history of recurrent cystitis. The findings of a recent pelvic examination were reportedly within normal limits. She owned a dog that frequently slept in her bed and the dog occasionally drank water from the commode. The patient had no occupational exposure to animals.

At that time her temperature was 38.5°C (101°F). On physical examination there was right costovertebral angle tenderness. A urinalysis showed four to six erythrocytes per high-power field (HPF), four to seven leukocytes per HPF, occasional bacteria and a positive leukocyte esterase test. A complete blood count showed 12,200 leukocytes per μl (67% segmented neutrophils, 12% bands, 13% lymphocytes and 8% monocytes). The patient took trimethoprim-sulfamethoxazole for one day before seeking treatment; a urine culture was not done. She was then treated for two weeks with oral administration of ampicillin, 500 mg four times a day.

(Mann BA, Quenzer RW: *Pasteurella multocida* urinary tract infection. West J Med 1987 Aug; 147:200-201)

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One week before admission, recurrent flank pain, fevers and chills developed. She continued to say she did not have lower urinary tract symptoms. She became febrile to 38.5°C, had rigors and was admitted to hospital.

On physical examination there was pronounced right costovertebral angle tenderness. Pelvic examination findings were not reported. Levels of serum electrolytes, urea nitrogen, creatinine and hemoglobin were normal. A leukocyte count was 12,000 per μl (69% segmented neutrophils, 13% band, 8% lymphocytes and 10% monocytes). A urinalysis showed a specific gravity of 1.020, pH 5.5, trace-positive leukocyte esterase, negative for nitrite, a moderate amount of blood, 6 to 12 erythrocytes per HPF, 20 leukocytes per HPF and a moderate amount of bacteria.

A regimen of amikacin, 500 mg given intravenously every 12 hours, and cephalothin, 1 gram given parenterally every 6 hours, was begun. Culture of urine specimens grew *Pasteurella multocida*, more than 100,000 organisms per ml; blood cultures were not done. This small gram-negative rod did not grow on MacConkey agar but on blood agar produced small, nonhemolytic, translucent colonies with a characteristic musty odor. The organism was indole-positive, and was differentiated and identified by the API 20E system. The organism was sensitive to ampicillin, cephalothin, gentamicin, tetracycline, trimethoprim-sulfamethoxazole, nitrofurantoin and nalidixic acid. After 24 hours of parenteral therapy, treatment was changed to cephradine, 500 mg given orally every six hours, for a total of two weeks. Urine cultures were sterile 48 hours after admission and her symptoms resolved.

A renal ultrasonogram showed normal kidneys with no hydronephrosis or hydroureter. On excretory urography there was focal cortical loss of the left kidney (overall size 12.5 cm), consistent with old pyelonephritis. The right kidney was enlarged and ptotic (14 cm), suggesting acute pyelonephritis. The study findings were otherwise unremarkable. A cystogram showed a large-capacity (450 ml) bladder without vesicoureteral reflux.

The patient became afebrile and was discharged on oral cephalosporin therapy. Follow-up cultures ten days after completion of therapy were negative, and the patient remained free of symptoms four weeks after discharge.

Comment

Pasteurella multocida commonly causes disease in animals. It can be isolated from the upper airways of as many as 54% of dogs and as many as 70% of cats.[2-4] Infections in humans are usually related to animal bites and scratches and remain localized, but a variety of complications including septicemia and distant infectious foci have been reported.[1,5,6] Unusual human infections described with this organism include pneumonia, meningitis, brain abscess, epiglottitis, peritonitis, liver abscess, appendiceal abscess, puerperal sepsis, septic arthritis, osteomyelitis and bacteremia.[7,8]

Infections by *P multocida* of the urinary tract are rare, occurring in chronically ill patients. Hubbert and Rosen described a total of 253 cases of *Pasteurella* infections unrelated to animal bites; in only 5 of these cases was the organism identified in a urine specimen.[9] Komorowski and Farmer reported two cases of urinary infection due to *P multocida*.[10] A 15-year-old boy in chronic renal failure with an ileal loop[11] and a 26-year-old woman with cervical carcinoma complicated by vesicoureteral reflux and renal failure[2] have been reported to have *P multocida* urinary tract infections.

The reason infection with this unusual organism developed in our patient is not clear. Decreased host defenses and major structural abnormalities characterize all previous cases but were not present in our patient. Results of her radiographic and ultrasonographic studies suggested previous pyelonephritis, so we cannot say her urinary tract was unequivocally normal. But it lacked major structural abnormalities, such as vesicoureteral reflux, that would predispose to infection. We have no reason to suspect a primary bacteremia with secondary seeding of the kidney.

The source of the organism is also of interest. *P multocida* organisms have been identified in the upper respiratory tract of healthy persons and patients in hospital.[10,12] Most patients with *Pasteurella* urinary tract infection have been in proximity to dogs or cats and some investigators speculate contact with these animals as a source.[3,11] The female genitalia may serve as a focus of infection—vaginitis, cervicitis and Bartholin's gland abscess have been reported.[2,3,5] There are no data on the role of intentional or accidental direct contact with oral secretions of animals. While there are a few reports of medical consequences of bestiality,[13,14] we could find no literature relating this unusual practice to urinary tract infections. Bestiality was not suspected in this case. Direct contact with oral secretions may not be necessary to cause infection, as the organism can be dormant for long periods.[2] Our patient's dog frequented both her bedroom and her bathroom. The dog's oral cavity was culture-positive for a heavy growth of *P multocida*, and it may have been the source of the infection.

Treatment is uncomplicated in most cases. A characteristic of *P multocida* is its sensitivity to penicillin.[10] Reported cases have responded to penicillin,[10] gentamicin[11] and trimethoprim-sulfamethoxazole therapy.[2] Why our patient's symptoms recurred after a two-week course of ampicillin is not known, but it may reflect a failure of nonparenteral antimicrobial therapy in upper urinary tract infections or patient noncompliance. Moreover, the role of individual antibiotics in this case is obscured by the patient's receiving multiple antibiotics. Her rapid defervescence after parenteral therapy and her uneventful recovery suggest that treatment of *P multocida* urinary tract infections should be straightforward.

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Disseminated Actinomycosis

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ACTINOMYCES ISRAELII, a normal constituent of oral flora, is an opportunistic organism requiring interruption of the mucosal barrier to be pathogenic.[1] Most commonly, actinomycetic organisms burrow without regard for facial tissue planes, resulting in draining sinuses and masses of abundant granulation surrounded by dense fibrous tissue. The following is a report of a case of disseminated actinomycosis presenting with nonspecific constitutional symptoms and radiographic findings. This case shows the indolent nature and diagnostic challenge of this disease.

Report of a Case

The patient, a 41-year-old man with a history of schizophrenia, presented for evaluation of anemia, weight loss and cough. He was well until 1983 when he sustained a massive upper gastrointestinal hemorrhage requiring a vagotomy and subtotal gastrectomy. He recovered without complications and did well until July 1985 when his hematocrit was noted to be low and unresponsive to iron, folate and vitamin B_{12} therapy. Chest x-ray and barium enema films were normal. In addition, he had a six-month history of weight loss and a nonproductive cough for one week. He smoked heavily but said he did not have tuberculosis or chemical exposures and did not abuse drugs intravenously. Findings of a physical examination were significant for cachexia, extremely poor dentition, pulmonary bibasilar rales and right upper quadrant abdominal tenderness. A stool specimen was heme-negative. Laboratory studies elicited the following values: hemoglobin 8 grams per dl, hematocrit 24.6%, leukocyte count 12,600 per μl (65% polymorphonuclear neutrophils, 22% bands), platelets 754,000 per μl, erythrocyte sedimentation rate 143 mm per hour, prothrombin time 14.6 seconds (11.9, control), total protein 9.1 mg per dl, albumin 1.7 mg per dl, alkaline phosphatase 159 units per liter (Westergren), serum aspartate aminotransferase (glutamic-oxaloacetic transaminase) 28 units per liter and serum alanine aminotransferase (glutamic-pyruvic transaminase) 20 units per liter. A chest x-ray film showed many nodular lesions 0.5 to 2.5 cm in diameter predominantly in the lower lung fields (Figure 1). A blood smear showed 1+ macrocytes and microcytes with 2+ rouleaux.

Bronchoscopy and a transbronchial biopsy specimen showed nonspecific inflammation without granulomas. A smear was negative for acid-fast bacilli, and the patient was anergic to skin tests. The patient's condition continued to deteriorate, with daily fevers to 39.4°C (103°F), and his hematocrit dropped to 21%. A bone marrow aspirate and biopsy specimen, taken on day 3 of admission, showed a decreased erythroid series and a normal plasmacyte popula-

(Hennrikus EF, Pederson L: Disseminated actinomycosis. West J Med 1987 Aug; 147:201-204)

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tion at 5% to 10%. Serum protein electrophoresis showed a broad band polygammopathy. A serum iron concentration and total iron binding capacity were 12 and 150 μg per dl, respectively, consistent with anemia of chronic disease. Cultures of blood, bronchial biopsy and bone marrow specimens remained negative.

An abdominal ultrasonogram showed many echodense areas of the liver, and a subsequent abdominal computed tomographic (CT) scan revealed many hypodense masses in the liver (Figure 2). On day 12 a percutaneous fine-needle aspirate of the liver initially showed a predominance of inflammatory cells—mostly histiocytes and lymphocytes consistent with chronic inflammation without evidence of malignancy. The patient was evaluated for an open-lung biopsy; on reexamination of the liver biopsy specimen, however, yellowish granules were noted and subsequent stains showed numerous colonies of gram-positive non-acid-fast filamentous branching rods consistent with *Actinomyces israelii* (Figure 3). Anaerobic cultures grew several species of *Bacteroides* and *Fusobacterium*, but no *Actinomyces*. The patient received penicillin, 2 million units given intravenously every four hours, and became afebrile within 48 hours.

A barium enema study showed a cone-shaped pouch at the hepatic flexure extending superiorly and ending blindly without extravasation of barium (Figure 4). No other irregularities were noted and an upper gastrointestinal series was unremarkable.

The patient received a four-week course of penicillin given intravenously, followed by a five-month outpatient course of penicillin by mouth. He remained afebrile, was without pulmonary symptoms and began to gain weight. On discharge his hematocrit was 27% and his chest x-ray film had cleared.

Discussion

Although *Actinomyces*—from Greek for "ray" and "fungus"—was named in 1878 to describe the filaments radiating from a central tangled mass, it was later (1960) identified as an obligate anaerobic or microaerophilic bacterium.[2] It is a fastidious, weakly gram-positive, non-acid-fast, branching filamentous rod. In an abscess the outer zone of granulation surrounds a center of "sulfur granules," named for their grossly yellow appearance but consisting of entangled masses of the organism contained within a protein-polysaccharide complex that under the microscope is in a ray form, giving a sunburst appearance.[3] The organism is difficult to culture[4,5] and is rarely encountered as a pure isolate. Brown reviewed 181 case records of actinomycosis microscopically confirmed based on lesions with granules of gram-positive branching bacilli seen with a Brown-Brenn

Figure 1.—Chest x-ray films, posteroanterior **(top)**, and lateral **(bottom)**, show bibasilar multinodular infiltrates.

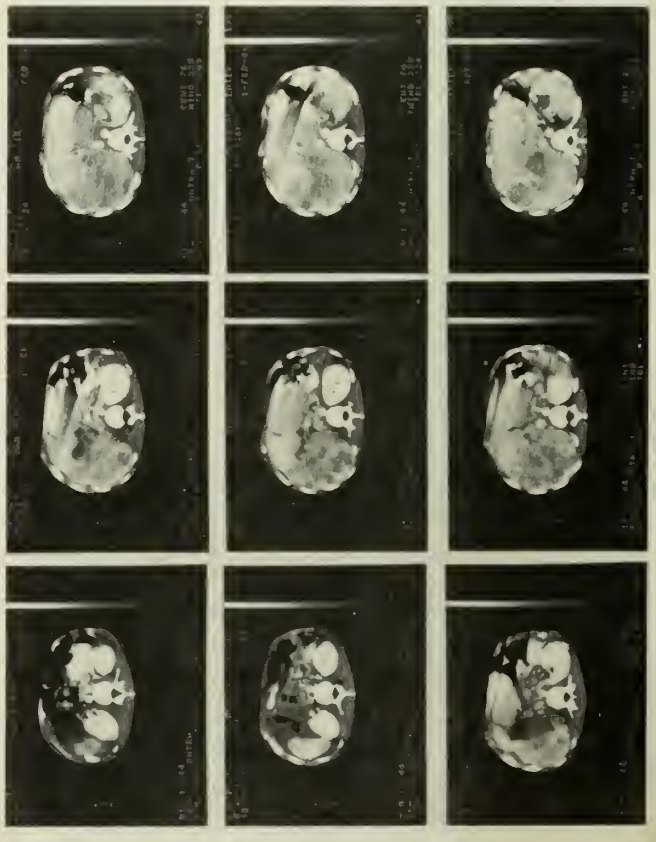

Figure 2.—An abdominal computed tomographic scan shows multiple hypodense masses throughout the right lobe of the liver.

stain. Of the 67 attempted cultures, only 24% were positive for actinomycosis, 46% showed no growth and the rest grew various other bacteria.[6] Holm examined specimens of pus from about 650 patients with closed actinomycotic lesions, and in all instances other microbes were present, particularly coliforms and gram-negative anaerobic bacilli in abdominal sources, and corroding *Bacillus* and *Actinobacillus actinomycetemcomitans* (constituents of oral flora) in pulmonary sources.[7] Successful identification requires careful handling, culturing many specimens in enriched media under anaerobic conditions and carbon dioxide and an adequate time (five to ten days) for growth. Therefore, a definitive diagnosis is usually made on histologic identification of an actinomycotic granule and occasionally by culture. Our diagnosis was made histologically with Grocott's methenamine-silver and Brown-Brenn stains.

Human actinomycosis has five clinical presentations: cervicofacial, thoracic, abdominal, disseminated and pelvic—the last associated with intrauterine contraceptive devices.[8] In Brown's review of 181 patients presenting with the first four types, he found a proportion of about 45%, 25%, 20% and 10%, respectively. The disease can smolder for as long as 15 years before a diagnosis is made; Brown found, however, that 90% were diagnosed one month to two years after the initial symptoms.[6]

Antecedent factors are frequently evident. A dental infection or a manipulation commonly precedes a cervicofacial disease.[4] Aspiration, esophageal penetration or direct extension from the neck and mediastinum can result in a thoracic infection.[3] Disruption of the intestinal mucosa from an appendectomy, gastrectomy, cholecystectomy, diverticulitis, cancer or trauma (blunt or penetrating) can lead to an abdominal infection.[4,5,9,10]

Hematogenous dissemination apparently stems most frequently from an initial pulmonary infection.[11-13] One reason for this association may be the lengthy delay in diagnosis of pulmonary actinomycosis. The clinical picture often mimics tuberculosis or malignancy with nonspecific constitutional symptoms of weight loss, cough, chest pain, fever and hemoptysis going unrecognized until an empyema or chest wall fistula develops.[3] Therefore, this delay in diagnosis and consequently prolonged disease state theoretically provide adequate time for dissemination. The liver is the other organ most commonly involved in disseminated disease, but because isolated hepatic cases are seldom seen, it is more likely that the liver is secondarily infected.[6] Possible mechanisms of hepatic involvement include direct extension from the intestinal wall, portal vein delivery from an infected appendix or colon or hepatic artery transport during general dissemination.[3,14]

Patients present with fever, weight loss, anorexia, nausea,

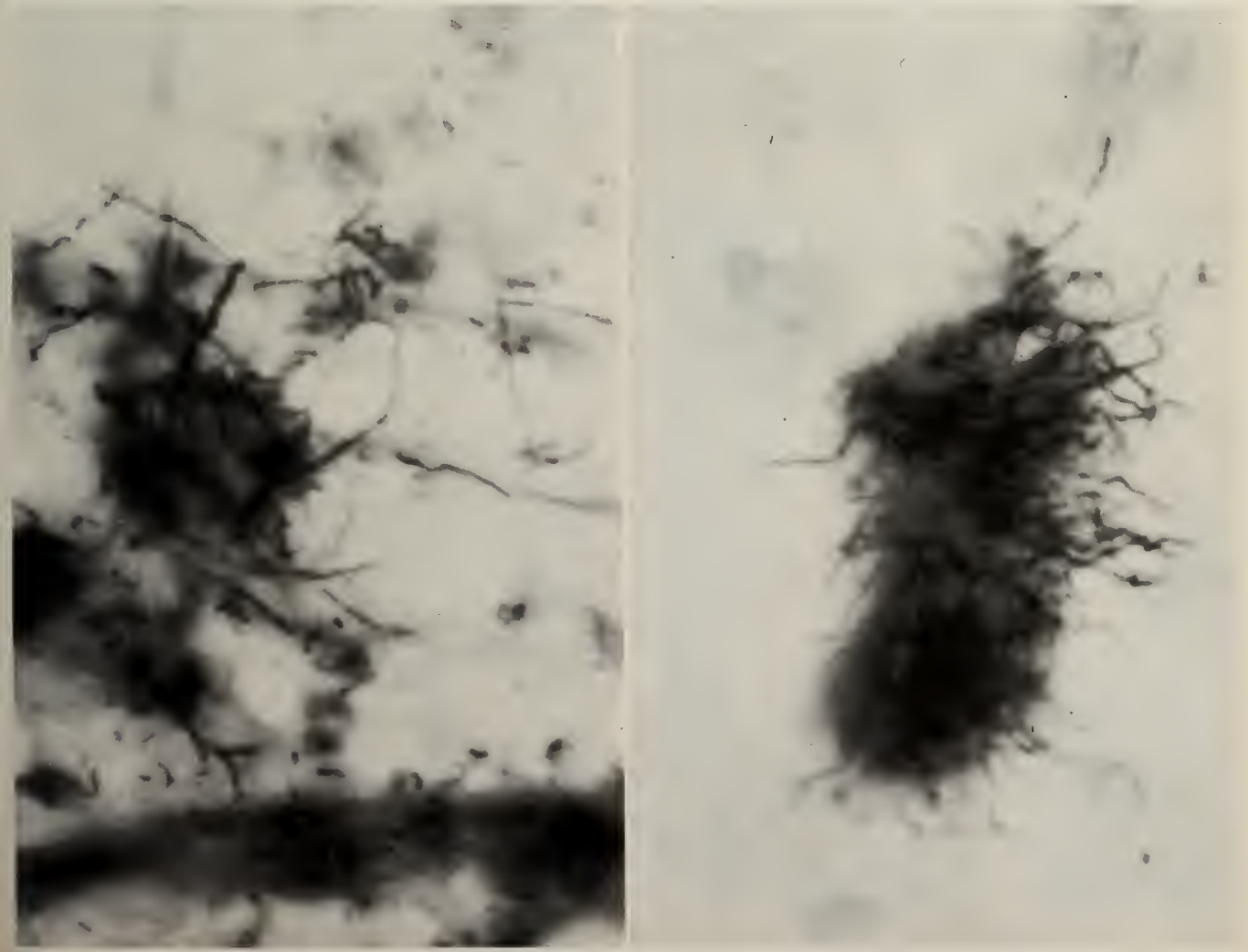

Figure 3.—Microphotographs of a liver biopsy specimen show (**left**) gram-positive, branching filamentous bacilli (Brown-Brenn stain, original magnification × 1,000) and (**right**) a sulfur granule of actinomycosis (Grocott's methenamine-silver stain, original magnification × 1,000).

vomiting and fatigue. A history of temporary resolution of symptoms following a short course of penicillin may be helpful in suspecting *Actinomyces*. Without the presence of a sinus tract or fistula the diagnosis is very difficult. In one series the correct diagnosis was made in only 7% of patients at the time of admission.[4] The differential diagnosis includes miliary tuberculosis, other granulomatous diseases, neoplasm with or without metastases, appendicitis, cholangitis or regional enteritis, especially if sinus tracts are present.

Our patient presents a confusing picture. His poor dentition, which eventually required total dental extraction, is a likely source for pulmonary infection via aspiration of oral secretions. On the other hand, his previous gastrectomy and the cone-shaped colonic pouch resembling a fistula lead one to suspect intestinal trauma as the cause of the hepatic lesions. No evidence of fistulous tracts through the diaphragm could be found to incriminate direct extension between the liver and lung. Therefore, two possibilities exist: a heavily infested oral cavity seeding the lung and the bowel separately or, more likely, hematogenous spread from either a pulmonary or an intestinal primary source, secondarily infecting the liver.

Laboratory findings are also nonspecific: leukocytosis, normohypochromic, normocytic anemia, an elevated erythrocyte sedimentation rate, an increased γ-globulin level,[15] a slightly increased alkaline phosphatase value and thrombocytosis.[16,17] Radiographically, pulmonary involvement can take the form of a mass, chronic fibrocavitary or chronic alveolar infiltrates ranging from a small patch to complete involvement of a lung.[18] Pleural involvement occurs in most cases, evident as an effusion, empyema or pleural thickening. Although less frequent, suspicion is raised with chest wall invasion—soft tissue swelling, draining sinuses, wavy periostitis, rib destruction and with penetration of an interlobar fissure.[18] Actinomycosis of the liver appears as multiple focal defects by technetium Tc 99m sulfur colloid and as intense focal concentration by gallium citrate Ga 67 nuclear medicine scans. This pattern is also seen with malignant neoplasms, lymphomas and pyogenic abscesses.[19] A CT scan in our case showed many hypodense areas in the liver, again a nonspecific finding but an aid in localizing an area for biopsy.

Figure 4.—A barium enema film shows surgical wire in the left upper quadrant and a colonic cone-shaped pouch extending up from the hepatic flexure, resembling a fistulous tract.

Cedermark and co-workers reported a very similar case of a possible neoplasm of the liver with pulmonary metastases.[16] Their patient underwent exploratory laparotomy and hepatectomy of the left lobe to remove a large mass, later histologically proving to be *Actinomyces*. We avoided a surgical procedure in our patient by using CT-guided fine-needle aspiration of one of the hepatic masses. Meticulous examination of the specimen by our pathologist revealed the characteristic sulfur granules and branching rods.

The effectiveness of the use of penicillin in treating actinomycosis is well established.[4] Recommended courses of therapy vary considerably, but it is generally accepted that treatment of disseminated disease must continue for a long period of time. Initial treatment is usually high doses of penicillin given intravenously—10 to 20 million units per day for two to six weeks—followed by penicillin taken orally—2 to 5 million units per day—for three to six months.[3] Tetracycline (the preferred agent), lincomycin, clindamycin, chloramphenicol and chlortetracycline hydrochloride (Aureomycin) in penicillin-allergic patients have been used successfully but aminoglycoside activity is negligible.[2] Surgical excision and drainage may be necessary when antibiotic therapy proves inadequate.[9]

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Correspondence

Causes of Anosmia

TO THE EDITOR: Davidson and co-workers evaluated 63 patients at their Nasal Dysfunction Clinic.[1] None of these had nasal polyps. Yet, it seems, this is a most common (if not the most common) cause of anosmia. It is easily diagnosed and frequently associated with allergic rhinitis and asthma.

Perhaps the reason none of their 63 patients had nasal polyps is that only difficult puzzling cases were referred to their clinic. Yet nasal polyps and anosmia are so common that the readers should be cognizant of this fact and search for nasal polyps before looking further for a cause of the patient's smell dysfunction.

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1. Davidson TM, Jalowayski A, Murphy C, et al: Evaluation and treatment of smell dysfunction. West J Med 1987 Apr; 146:434-438

* * *

TO THE EDITOR: I read with interest the article "Evaluation and Treatment of Smell Dysfunction" by Terence M. Davidson, MD, and colleagues in the April issue.[1]

I recently saw a patient with long-standing asthma and rhinitis in whom progressive and insidious anosmia developed which turned out to be related to a baseball-sized frontal lobe meningioma. Frontal lobe tumors have been associated with anosmia.

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1. Davidson TM, Jalowayski A, Murphy C, et al: Evaluation and treatment of smell dysfunction. West J Med 1987 Apr; 146:434-438

The Plight of Public Hospitals

TO THE EDITOR: The complexities involved in delivering quality graduate training to medical students were well described by Gerbert and co-workers in their recent article.[1] Unfortunately, the unique dilemmas that public teaching hospitals are suffering in that regard were not adequately addressed. The accompanying editorial also stressed the impact of changes in funding for graduate medical education on private institutions.[2] In California, however, where public hospitals provide such functions to a very large portion of graduates, the greatest impact is on them rather than the private academic centers.

Public hospitals traditionally care for the largest number of poor patients and rely heavily on state or local governmental funding for both patient care and for educational activities. To compound the problem, private hospitals, for all the reasons described by Gerbert, are reducing the share of their resources devoted to charitable care or bad debts. Consequently, poor people are being forced out of the private institutions back to our public hospitals.

Faced with this ever increasing number of poor and uninsured patients and forced to care for them at reduced federal and state payment levels with limits on the amount of charges that can be allocated to graduate medical education places such institutions in an ever increasingly compromised position.[3,4]

Unfortunately, they do not have the option of securing larger numbers of paying patients to offset the costs of providing more care for nonpaying patients. As Gerbert so succinctly outlined for the private hospital, the public teaching hospital likewise has an even greater difficulty reducing its costs to compete with the private nonteaching hospitals. This has been an historical fact which prevails even today. Yet, as an academically affiliated health care center, we are expected to expose the graduates to the latest technological advances in medicine, to provide them with access to state-of-the-art laboratory tests, to give them opportunities for doing clinical research, to offer community-based physicians exposure to continuing education opportunities and to maintain a quality of patient care that is at least equal to community standards—all of this without placing undue additional burdens on the taxpayer.

Since care to the poor remains our primary commitment, which we morally will not and legally cannot abandon and to which our monetary resources must be primarily directed, economic stresses may increasingly jeopardize a public institution's commitment to its educational activities.

As identified in a recent Commonwealth Fund Task Force report on Academic Health Centers, one must first accept that public hospitals are not likely to obtain increased appropriations to compensate for an increased load of poor, uninsured patients.[5] Therefore, the only sources available to support this increased patient load will be redistribution of available funds away from other areas of expenditure. Two obvious areas come to mind. First, there may be a reduction in medical school faculty to staff the hospital. Second, the institution might be forced to reduce or abandon its educational functions. Neither of these should be permitted to happen. The presence of full-time medical school faculty to supervise trainees has been historically shown to assure not only an improved education for them but also has increased the quality of care given to the patients. Arguably, the care is more expensive but not necessarily more than if that same training were carried out in a private institution. Physicians in graduate training programs, regardless of the training site, are essentially performing apprenticeships, analogous to training in industry, who then become "journeymen" physicians. Apprentice programs in industry are characteristically also expensive operations. To reduce or abandon graduate training programs is also not an effective solution. Ample data have been presented supporting the contention that too many physicians are being trained. Since public hospitals in California produce the largest number of graduates, one could argue that those are the very institutions that should make reductions in their training programs. I do not agree. In my opinion, large public teaching hospitals and their clinics still remain the single best learning resource for graduate physicians. Graduates are exposed to a wide variety of patients and diseases requiring primary as well as other care, including patients similar to those seen at tertiary private institutions. To replace this wealth of patient resource in the private sector, the training programs would clearly have to decentralize their educational efforts to hospitals and ambulatory sites with a sufficient concentration of patients to assure that graduates are exposed to an adequate number of patients with a diverse spectrum of diseases. In rebuttal, smaller private institutions argue that it is not the number of patients seen but the quality

of teaching and learning with each patient seen that is important. In a sense that is true for common illness but not when one wishes to learn about the less common disorders. The larger, especially public, institutions have the advantage, evidence for this being beyond the scope of this communication.

How then can a public teaching hospital cope with this increasing financial strain and yet preserve its graduate education programs? One possible solution might be that as private teaching hospitals reduce their care to the poor and uninsured patients, they must also reduce or eliminate their graduate teaching programs. Some of the funds saved could be redistributed to public teaching hospitals for their graduate education activities which might include sending their trainees to private institutions for portions of their training. This is already being done effectively by many academic health centers and medical schools. Additional financing for graduate medical education could be provided by any or all of the following: (1) The private sector and all health insurance programs should be asked to participate in this function, not just federal, state and local governmental agencies. (2) Although politically unpopular, all alcohol, tobacco and ethical drug products should be taxed, with the proceeds earmarked for health care, a portion of which could be used to support graduate medical education. (3) The academic health centers should seek private funding through grants and endowments to support graduate medical education to the same extent that research support is now funded.

As in all other fields of medical care, graduate medical education is not only being subjected to programmatic stresses but is also being threatened by economic hardship. Characteristically, the academically affiliated public hospitals are experiencing the greatest negative impact. Measures must be taken by all those concerned in order to preserve the high quality of training programs from which this country has benefited for many years.

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Medicare-Funded Cardiac Transplants

To the Editor: The article by Renlund and associates in the May issue[1] details the successful experience of a cardiac transplant center that would not qualify for funding under Medicare's proposed guidelines.

We are specifically concerned that the designation of *only* a few centers will have an adverse effect on other successful programs. If third-party payers adopt these recommendations and only reimburse at those federally designated centers, 76 of the 86 centers that presently perform cardiac transplantation would not be able to continue to do so. Further, with the low minimal survival rates that have been recommended, and the three-year length of time for a program to prove itself successful, we feel the Department of Health and Human Services is inappropriately emphasizing the quantity of transplants performed versus the quality or survival rates of different programs.

As one of the four most active cardiac centers in California, our program has performed 18 transplants over a 19-month period with a 100% survival rate to date. We have worked diligently at establishing a multidisciplinary and successful cardiac transplant program that is committed to serving the people of San Diego County. In addition, a coordinated research effort at our institution to define noninvasive immunologic and hemodynamic correlates of transplant rejection has already yielded published results. We feel that our success in cardiac transplantation has important positive input both on health care delivery in our region and on transplantation in general.

We hope that Medicare closely evaluates their proposed guidelines before making them final, thus avoiding a negative impact on many programs. Highly successful transplant programs should continue to be supported.

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Heart Disease and Mortality

To the Editor: Regarding the recurrent discussion concerning dietary cholesterol in atherosclerosis, the most recent iceberg tipped on pages 621-622 in your May 1987 issue of the journal.[1,2] Both Dr Wolfstein and Dr Desmond are correct. Dr Desmond thinks she answers Dr Wolfstein's caveat by quoting the consensus conference in December 1984, and she quotes them accurately—that is, that they talked about "heart attacks." These data are now rather firm, especially with reference to the most recent study presented in the *American Journal of Cardiology* a year ago.[3]

Dr Desmond, however, incorrectly extrapolated the statement on heart attacks to mortality in her article in the January 1987 issue.[4] This is where Dr Wolfstein is right. Coronary artery disease mortality has not as yet been documented to be reduced by cholesterol lowering.

Pearce and Dayton many years ago in the Veteran's Administration Hospital study at Los Angeles showed that the death rate stayed about the same over a five-year study.[5]

Once again, arteriosclerosis is "the blindman and the elephant."[6]

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Physicians and the Death Penalty

To the Editor: In her article on "Physicians and the Death Penalty,"[1] Dr Thorburn raises issues that should not be ignored by any physician. Her assertions regarding the role of medical examiners deserve comment. In the most extreme position detailed in her article, Dr Thorburn implies that *any* involvement by physicians in *any* phase of a case leading to execution is unethical. This would mean that medical examiners should not examine homicide victims because of the potential for a death sentence. As medical examiners it is our responsibility to document injuries and present our findings in an honest and unbiased manner. In this we act as the advocate of the murder victim, not as an agent of the court. Our testimony can exonerate an innocent suspect as well as implicate the guilty. If we were to stop examining homicide victims there is the potential that our lack of involvement could lead to the death of an innocent person, a much more untenable ethical position.

In the case of medical examiner involvement after an execution we once again must act as the advocate of the deceased person. It is our duty to assure that the executed person has no injuries other than those which were legally sanctioned. Without our involvement there can be a question in the minds of the deceased's relatives as well as society as a whole as to whether the ultimate and irreversible sanction has been fairly and justly administered. It is our belief that to ban all participation of physicians in death sentence cases would raise greater ethical issues than it resolves.

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1. Thorburn KM: Physicians and the death penalty. West J Med 1987 May; 146:638-640

* * *

To the Editor: Dr Thorburn's "Informed Opinion" in the May issue of the journal[1] seems both informed and, quite clearly, an opinion. Her material is carefully arranged and very well documented, but the conclusion suffers from the incongruity that is unavoidable when attempts are made to apply pure idealism to an imperfect society. It is neither possible nor ethically defensible to declare that physicians must refuse to be involved in the insoluble problem of capital punishment. If more than 70% of the US citizenry views the death penalty as necessary for societal protection, it will certainly see to it that "dangerous" persons are executed, whether or not physicians choose to participate.

It is quite clear that society is not capable of controlling the small percentage of its members who are bent on destroying others. Because methods of incarceration are fallible and because it is quite clear that sociopathic personalities cannot be rehabilitated, execution looms as the logical, if unpleasant, societal recourse. It is specious to argue that it should not be done because it offends our sensibility or is often done imperfectly. Let those who argue so skillfully and emotionally that the death penalty is improper suggest a practical and reliable alternative to the control of persons like Ted Bundy, who have the form of humanity without a shred of human sensitivity, who are frighteningly skillful at escape and manipulation of the legal system and who have no allegiance whatsoever to the Universal Declaration of Human Rights.

Our recognition of rights and the commonality of basic human values constitute excellent guidelines for solving the majority of society's problems. But there are no rules that are applicable in every situation, and Dr Thorburn's proposal that it is unethical and indefensible for any physician to "participate in any act connected to and necessary for the administration of capital punishment" will create more problems than it will solve in our real world, where the issues present themselves in shades of gray. No amount of wishful thinking and idealistic pronouncement will convert them to black and white.

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1. Thorburn KM: Physicians and the death penalty. West J Med 1987 May; 146:638-640

Opposing Views on Deaths From Firearms

To the Editor: The March issue of the journal contains, under the heading "Special Article," an article with the strange title of "The Epidemiology of Firearm Deaths Among Residents of California."[1] This article not only lacks any scientific premise, but contains some gross errors of fact. Firearms deaths no more have an "epidemiology" than baseball bat or butcher knife deaths. This article is clearly an undisguised antifirearms propaganda piece having no place in a putative scientific journal. In the first paragraph the authors refer to "more than 30,000 Americans" alleged to die as the result of gunfire. The last figures I have seen, derived from the 1985 FBI annual report, indicates less than 20,000 firearms deaths, and it is imperative that this be understood to include all categories of firearms deaths including suicide and accidents. I am giving these numbers strictly "off the cuff" without available reference sources here in my office, but I am generally quite familiar with the numbers concerned here. My figures are approximations from memory. The under 20,000 figure above is correct as stated. As I recall, about 8,000 of these are suicide. Suicide is a psychiatric and psychologic problem, not a matter of methodology. Reference to firearm suicide is clearly a non sequitur, and I would only point out in passing that Japan, which virtually prohibits private ownership of firearms, has a far higher suicide rate than the United States, where in most localities firearms can be obtained with little difficulty and complicated impedances in others, which do not seem to affect suicide rates.

As I recall, some 3,000 or so firearms deaths are accidents. Accidents mostly happen as a result of ignorance or carelessness, whether we are talking about automobiles, lawn mowers, chain saws or firearms. It may be worth mentioning that there has never been a fatal accident to my knowledge on a firearms range operated by a rifle or pistol club affiliated with the National Rifle Association, clearly indicating that proper training and proper use is the answer here. It is also pertinent that the last fatality figures I have seen by the Na-

tional Safety Council list the shooting sports (hunting, target shooting and the like) as *15th* in rank behind such "safe" sports as fishing, boating and swimming.

Nowhere in the March article do the authors make any separation of homicides into its several very different categories. What about killing by gunfire by a policeman in the line of duty, or by a citizen in self-defense? The authors lump all this together as though someone being shot is necessarily a crime. Incidentally, I am surprised that the authors did not bring in the old, often repeated but unequivocally false, propaganda item that "citizens should not own firearms because criminals will take them away and use them against the citizens." The fact of the matter is that criminals are killed by citizens in self-defense at a rate three times that of policemen killing felons in the execution of their duty. These two categories of legal killing by firearms are lumped in with the criminal misuse of firearms.

At the very outset, the attempt of the authors to ascribe an epidemiology to inanimate mechanical devices is unscientific and has no merit in a medical journal. Quite predictably from the first paragraph, the authors toward the end of their article advise that "restricting the availability of firearms, and particularly handguns," is recommended. They do not tell the reader that there is a direct statistical correlation with highly restrictive gun control regulation and high crime rates including firearms. Washington, DC, Detroit and New York all make it virtually impossible for private citizens to own firearms, particularly handguns. These are among the highest murder rate metropolitan areas, quite in contrast to Vermont, which has the lowest homicide rate in the country, and no restrictive firearms laws at all, including the right to carry a concealed weapon, at the last information I had.

Even beyond the United States, virtually all of the Latin American countries have very stringent controls on private ownership of firearms, and far higher homicide rates than the United States. It will undoubtedly surprise most everyone, as it did me, to learn that East Germany, behind the Iron Curtain and as rigidly a controlled police state as any among the Soviet puppet states, including prohibiting private ownership of firearms, has a higher homicide rate with firearms than the United States.

If the authors want to pursue some interesting facts from a sociologic standpoint, that is their business, and I would suggest first that they look into the fact that about two thirds of homicides in this country are committed by blacks (some 12% or so of our population). If these are deleted, the United States has one of the lowest rates of firearms homicides of any country in the world. Deaths from firearms accidents have been progressively decreasing on a per capita basis for many years. Suicides are a problem for the psychiatrists and the psychologists.

In short, this article lacks any scientific merit, is grossly inaccurate and is a patent propaganda piece having no place in a medical journal.

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REFERENCE

1. Wintemute GJ, Teret SP, Kraus JF: The epidemiology of firearm deaths among residents of California. West J Med 1987 Mar; 146:374-377

* * *

To the Editor: The publication of "The Epidemiology of Firearm Deaths Among Residents of California"[1] raised hopes that a scientific approach could be brought to bear on a significant health problem which has become so intertwined with the political implications of restrictions on firearms ownership that all logical thought has been lost in an emotional fog.

Unfortunately, there are strong elements of political polemic in the article which will again interfere with rational discussion of the issues. I refer to the statement, "firearms were the leading cause of intentional death in the state," whereas the facts are that firearms may have been the leading instrument of intentional death but identification of the causes lies elsewhere. This is not mere nit-picking, as is shown in the discussion section in which the authors point out that changes in motor vehicle design reduced the numbers of motor vehicle-related injuries and deaths right after noting that accidental shootings are of minor significance in the overall problem and presumably, therefore, changes in firearms design are not going to be of protective value. Instead, they make the logical leap to reducing the use of firearms in suicide by reducing the availability of firearms. No attention is given to the much greater rate of suicide in Japan which is an essentially firearm-free society. The point is of course that suicide is not caused by firearms but by the desire to end one's life, and in the absence of firearms, other means are found. Note, for example, the recent rash of teenaged deaths by carbon monoxide poisoning.

Last, the authors make reference to the "Saturday night special," a buzzword among those bent on eliminating firearms from our society, but a term which, as has been well demonstrated in Congressional hearings, has in fact no real meaning and no relevance to the use of firearms for suicide or any other purpose.

In summary, *The Western Journal of Medicine* has lent its prestige to the publication of a thinly disguised political polemic, and the real issues of the relationship of firearms ownership and availability in an increasingly urbanized and violent society are left unaddressed. Articles such as this belong in an editorial section, not published under the guise of scientific objectivity.

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1. Wintemute GJ, Teret SP, Kraus JF: The epidemiology of firearm deaths among residents of California. West J Med 1987 Mar; 146:374-377

* * *

Drs Wintemute, Teret and Kraus Respond

To the Editor: Your correspondents implicitly and explicitly question our epidemiologic approach to injuries, and firearm injuries in particular. They argue that behavior (a host attribute) is the only proper area for research; consideration of the agent, vehicle or environment is improper or irrelevant.

Epidemiology is "the study of the distribution and determinants of health-related states and events in populations, and the application of this study to control of health problems."[1] Drs Johnson and Howard's assertions notwithstanding, the knowledge that injuries can profitably be investigated using epidemiologic methods has existed since the time of Hippocrates.[2] In our own time, pioneers such as the late William Haddon, Jr, Susan Baker, Julian Waller and others have refined and applied this knowledge. We owe crashworthy cars (credited with saving more than 90,000 lives since the late

1960s), child-resistant containers (there are now fewer than 10 unintentional childhood poisoning deaths per year in California) and many other advances to the epidemiologic approach to injuries. A division of Injury Epidemiology and Control has been established at the Centers for Disease Control to further this work.

Dr Johnson has grossly underestimated the true number of firearm deaths occurring each year. His admission that he is working "strictly 'off the cuff' " does not excuse his disregard for accuracy. *Uniform Crime Reports,* the annual report on crime in the United States, published by the Federal Bureau of Investigation, reports only homicides.[3] The National Center for Health Statistics does collect information on all firearm deaths. In 1984, the most recent year for which they have data available, there were 31,091 firearm deaths in all: 17,120 suicides, 11,820 homicides, 1,668 unintentional deaths and 483 deaths for which intentionality remained undetermined (National Center for Health Statistics, unpublished data, April 1987).

Dr Johnson states that we have included shootings by police officers in our homicide results. He is wrong, as a more attentive reading of the Methods section of the article would have shown him. We have perforce included homicides classified as justifiable—such as a resident shooting a burglar in the act of committing burglary—or occurring in self-defense, as they are not treated separately in the vital statistics data base we used. These categories account for less than 2% of all homicides nationally, however, and only 2.3% of a series of nearly 400 firearm deaths occurring in the home where the weapon involved was kept.[4]

There is, in fact, substantial evidence that bringing a firearm into one's home makes that home a riskier place in which to live. Guns acquired recently for protection were involved in the majority of 80 childhood shootings in Detroit.[5] In Cleveland, firearms kept in the home were 6 times as likely to be involved in an unintentional shooting death as in the death of a criminal or an unknown intruder.[6] In Seattle, firearms kept in the home were "involved in the death of a member of the household 18 times more often than in the death of a stranger."[4] And here in California, the use of firearms for household protection has repeatedly led directly to fatal unintentional shootings of one child by another.[7]

In criticizing our use of epidemiologic methods, Dr Howard challenges our assertion that firearms are in themselves a cause of intentional death. While many factors contribute to the development of the intent to injure either oneself or another person, firearms are uniquely capable of translating that intent into a fatality. Assault with a firearm, for example, is six times as likely to have a fatal outcome as is assault with a knife.[8] Attempted suicide by firearm is 24 times as likely to result in death as is attempted suicide by ingestion.[9] This is very important, as both assaulters and suicide attempters appear in many cases to act on impulse, making use of whatever weapon comes most easily to hand.[10,11] Reducing access to a particularly lethal, easily available means of inflicting harm does not necessarily lead to a compensatory increase in the use of other means, and a reduction in deaths may result.[12]

Both correspondents agree, in sum, that "Guns don't kill people, people do." A more accurate statement, developed by Stephen Teret and articulated by Susan Baker, is, "People without guns injure people; guns kill them."[13]

Finally, both correspondents criticize our "politicization" of firearm deaths. This criticism is simply invalid. Increasingly the major health issues of our time—malnutrition, the acquired immunodeficiency syndrome and the prevention of nuclear war, for example—are being confronted in the public policy arena. The public health problem created by the widespread availability of firearms must be seen in this light. Physicians are morally obliged to work for the better health of their patients and communities at the policy level, as well as in individual patient encounters. As Virchow said, "medicine is a social science, and politics nothing but medicine on a grand scale."[14]

Other points raised, such as the racist suggestion that we simply ignore black homicide, need no rebuttal from us. We leave dealing with the aspersions cast upon the quality and integrity of the *Journal* to its editors.

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Topics in Primary Care Medicine

Clinical Significance and Interpretation of Antinuclear Antibodies

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Primary care physicians often see patients with rheumatic complaints such as joint pain, muscle weakness and other symptoms that suggest a "connective tissue" disease. When this occurs, there is a tendency to order a panel of tests that often includes the erythrocyte sedimentation rate, a fluorescent antinuclear antibody (FANA) test and a test for rheumatoid factor. The FANA test, in particular, is usually done as a "screening" test for systemic lupus erythematosus or one of the closely related systemic rheumatic diseases. Unfortunately, most clinicians do not have a clear understanding of how to interpret the antinuclear antibody test result. Complicating this issue even further is the fact that many clinical laboratories are now offering tests for antibodies to a variety of more specific nuclear antigens, such as antibodies to native (double-stranded) DNA (nDNA). When should a FANA test be done, what does it mean and how should it be interpreted? Moreover, when should the antinuclear antibody tests that detect unique nuclear antigens, such as nDNA, be done? In this brief review we summarize what is known about the clinical utility of the various antinuclear antibody tests that are currently available and provide suggested guidelines for their use.

Biology of Antinuclear Antibodies

Antinuclear antibodies are a spectrum of autoantibodies that react with various nuclear molecules, including DNA, ribonucleic acid (RNA), histones, acidic nuclear proteins or complexes of these molecular elements. The presence of antinuclear antibodies in serum appears to be associated with various factors including genetic predisposition (such as the histocompatibility locus DR3), environmental agents (ultraviolet light, viruses, certain drugs and chemicals and intravenous drug use), estrogen-androgen balance, chronic infections, neoplasms and advancing age. Aging cannot be overemphasized as a factor associated with the presence of antinuclear antibodies. One recent study noted that 18% of otherwise healthy persons older than 65 years had a positive—that is, a titer of more than 1:10—FANA test. While clinicians generally associate the presence of antinuclear antibodies with a rheumatic disease, particularly systemic lupus erythematosus, these antibodies can also be detected in persons with other immunologically mediated diseases such as Hashimoto's thyroiditis and immunopathic chronic active hepatitis.

While there is some evidence that antibodies to nDNA and other antinuclear antibodies may play a direct role in the pathogenesis of nephritis in patients with lupus erythematosus, their pathogenic role in the rheumatic diseases is poorly understood. Although recent research characterizing the nature and disease associations of the nuclear antigens to which various antinuclear antibodies are directed is exciting and may eventually provide insight into the pathogenesis of various autoimmune diseases, this information is of little practical use to clinicians. Therefore, tests for antinuclear antibodies are most often used as aids in the diagnosis and management of disease.

General Principles of Test Interpretation

When considering the possibility of doing an antinuclear antibody test, clinicians should keep certain general principles of testing in mind. (For a more detailed discussion of these principles, see the article by Sox.) First, if the result of a test will have no effect on any patient-management decision, the test should not be done. In the case of antinuclear antibody testing, it should be stressed that the diagnosis and management of most systemic rheumatic diseases rest primarily on clinical manifestations and the results of more routine laboratory tests.

Second, if the sensitivity and specificity of a test are known, after estimating the chance (pretest probability) that a patient has a specific disease, such as systemic lupus erythematosus, it is possible to apply Bayes's theorem and calculate the effect of a positive (or negative) test result on the posttest probability (see Table 1 for definitions). Whereas few physicians think in such a quantitative fashion, two important generalizations can be easily remembered and applied:

(White RH, Robbins DL: Clinical significance and interpretation of antinuclear antibodies. West J Med 1987 Aug; 147:210-213)

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ABBREVIATIONS USED IN TEXT

FANA = fluorescent antinuclear antibody
nDNA = native DNA
nRNP = nuclear ribonucleoprotein
RNA = ribonucleic acid

- When a patient has a low but appreciable probability of having a particular disease, such as 5% to 40%, a test of high specificity, when positive, is helpful in establishing the diagnosis—that is, increasing the posttest probability.
- When a patient has a moderate to high probability of having a particular disease, a test of high sensitivity, when negative, is useful in excluding this disease—that is, decreasing the posttest probability.

As the sensitivity and specificity of a test diminish, the usefulness of the test also diminishes.

The third principle is that any test that falls short of being 100% specific should not be used indiscriminately to screen patients who have a low pretest probability of disease, as it is likely that a positive result will be "false-positive" rather than "true-positive." Stated another way, the ability of a positive test result, by itself, to accurately predict the presence of disease (positive predictive value) is critically dependent on the prevalence (pretest probability) of the disease in the population being tested. An example that illustrates this principle is the use of the FANA test to screen patients for lupus erythematosus. Several studies have shown that in a group of "healthy" persons between the ages of 20 and 40 years, about 1% of the population has a positive FANA test without apparent disease (the specificity for systemic lupus erythematosus = 99%), and it is known that 95% of patients with lupus erythematosus have a positive FANA test (sensitivity = 95%). Assuming that the prevalence of the disease in this group is about 1 in 700, a positive FANA test will accurately reflect the presence of lupus in only 13% of cases (seven false-positive results for every single true-positive result). Interestingly, if a FANA test is done on a more select group of persons, such as patients with polyarthritis, the predictive value of a positive FANA test in detecting lupus does not increase. This is because the specificity of a FANA test for the disease in this population is significantly lower (specificity = 50% to 70%) because patients with rheumatoid arthritis and other inflammatory arthritides frequently have a positive FANA test. Assuming that the prevalence of systemic lupus erythematosus in patients with polyarthritis is 1 in 20, the predictive value of a positive test is still less than 15%.

The fourth principle to remember is that the initial estimates of the specificity of a test for a particular disease usually overestimate the true specificity. This is because the patients selected for these studies usually have well-defined "classic" disease, whereas the "control" cases are usually healthy persons or patients in hospital in whom the prevalence of false-positive test results is low. A more ideal "control" group to study to define the specificity of a test would be a group of patients presenting with signs or symptoms suggesting the disease in question, such as joint pain, skin rashes and so forth. This is particularly the case for the rheumatic diseases.

The FANA Test

Most physicians are familiar with the general principles that underlie the indirect immunofluorescence technique, which is the most widely used method of detecting antinuclear antibodies. While rat and mouse liver and kidney were commonly used cell substrates in the past, human epithelial cell lines, particularly the KB and HEp-2 cell lines, are currently the most commonly used substrates. It is important to know that methodologic differences and particularly differences in the substrates used—such as HEp-2 cells versus mouse kidney cells—may lead to differences in FANA test results from different laboratories. A report of a FANA test generally includes the pattern of staining and the highest serum dilution (titer) that has detectable antibody.

FANA Titer

The titer of the FANA test that should be interpreted as "positive" varies from one laboratory to another and should be noted on the report slip. In patients with a well-defined rheumatic disease, the titer of the FANA test varies widely. For example, about a third of patients with lupus erythematosus will have a FANA titer of 1:40 or less, whereas a third will have a titer of 1:360 or more. The titer is not helpful in predicting the activity of any rheumatic disease. While most false-positive FANA tests are low titer and most high-titer tests are associated with clinically obvious disease, there may be no discernible disease in some patients who have a high-titer FANA test.

Antinuclear Antibody Patterns

The most common patterns of nuclear fluorescence reported and the specificity of each of these patterns are listed in Table 2. With the exception of the rim pattern, the pattern of nuclear staining lacks sufficient specificity to be diagnostically useful. There is often interobserver variation in pattern interpretation, and the pattern can vary as the test serum is

TABLE 1.—*Definition of Terms*

Sensitivity: Percentage of patients with a particular disease who have a positive test*

Specificity: Percentage of patients who do not have the disease who have a negative test†

Positive predictive value of a test for a disease:
(number of true-positives)/
(number of true positives) + (number of false-positives)

Bayes's theorem: A mathematical formula for calculating the effect of a positive (or negative) test result on the posttest probability of disease using the pretest probability of disease and the sensitivity and specificity of the test

*The true-positive rate.
†The true-negative rate = 1 − (the false-positive rate).

TABLE 2.—*Specificity of Commonly Reported Immunofluorescent Antinuclear Antibody Patterns**

Pattern	*Specificity*	*Seen in Patients With*
Homogeneous	Low	SLE, drug-induced SLE, RA, vasculitis, polymyositis
Speckled	Low	SLE, MCTD, Sjögren's syndrome, scleroderma, polymyositis, RA
Nucleolar	Low	polymyositis, scleroderma, vasculitis, SLE
Rim	High	SLE (98%), occasionally noted in patients with other rheumatic diseases

MCTO = mixed connective tissue disorder, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

*Sensitivity of a positive fluorescent antinuclear antibody test, any pattern: SLE = > 95%, drug-induced SLE = 100%, RA = 30% to 50%, Sjögren's syndrome = 75% to 80%, MCTO = 100%, scleroderma = 55% to 70%, dermatomyositis-polymyositis = 30% to 40%, vasculitis = 30%, Raynaud's phenomenon = 30%.

diluted because antibodies directed to several different nuclear antigens may be present in the same serum specimen.

A rim pattern is strongly associated with antibodies to nDNA. Homogeneous fluorescence is associated with antibodies directed against nuclear histone or DNA-histone complexes. A speckled antinuclear antibody pattern is associated with antibodies to acidic nuclear proteins and RNA-protein complexes, such as nuclear ribonucleoprotein (nRNP). A large-speckled pattern may be reported in patients who have anticentromere antibodies. A nucleolar pattern is associated with antibodies to elements that make up this organelle. The sensitivity of a positive FANA test in various diseases is also listed in Table 2.

Interpreting the FANA Test

There are only three diseases that include or require a positive antinuclear antibody test in their diagnostic criteria. The first is systemic lupus erythematosus. It is generally accepted that greater than 95% of patients with this disease will have a positive antinuclear antibody test and that more than 85% will have a positive FANA test two dilutions above the lowest titer that is acceptable as being "positive." In addition, virtually 100% of patients with mixed connective tissue disease and drug-induced lupus erythematosus have a positive antinuclear antibody test. Because the sensitivity of the FANA test in detecting these diseases is high, if clinical and laboratory findings suggest the presence of lupus erythematosus, mixed connective tissue disease or drug-induced lupus, a FANA test should be done. A negative test essentially *excludes* any of these diseases. As outlined earlier, a positive FANA test by itself is not diagnostic. In patients who have signs or symptoms compatible with either of these three disorders, however, a positive FANA test does increase the posttest probability that they have the disease.

Tests for Antinuclear Antibodies to Individual Nuclear Antigens

A variety of methods is available for detecting antibodies to individual nuclear antigens. As the number of different methods used to detect specific nuclear antigens has increased, a wider spectrum of patients than previously suspected has been noted to have low or moderate titers of antibodies to one or more of these nuclear antigens. The best characterized antinuclear antibodies and the specificity and sensitivity for the most common rheumatic diseases are listed in Table 3.

Antibodies to nDNA

The 1982 revised American Rheumatism Association criteria for classifying patients with systemic lupus erythematosus include, in addition to a positive FANA test, "an immunological disorder," which is satisfied if there is an elevated titer of antibody to nDNA *or* a positive lupus erythematosus preparation *or* antibodies to the Smith (Sm) antigen *or* a biologic false-positive serology test for syphilis. In some patients, the level of antibodies to nDNA varies directly with

TABLE 3.—*Sensitivity and Specificity of Antibodies to Nuclear Antigens*

Antinuclear Antibody	*Sensitivity*	*Specificity*	*Disease*
Anti-nDNA	SLE 60% to 70%	High	SLE (>90%) if present in high titer
Antihistone	Drug-induced SLE 100%, RA 15% to 20%, SLE 30%	Low	
Anti-Sm	SLE 30% to 40%	High	SLE 98%
Anti-nRNP	MCTD 100%, SLE 30%, scleroderma 20% to 30%, rheumatoid arthritis 10%, discoid lupus 20% to 30%	Low	
Anti-Ro (anti-SSA)	SLE 30% to 40%, Sjögren's syndrome 60% to 70%, RA 10%	Low	
Anti-La (anti-SSB)	SLE 10% to 15%, Sjögren's syndrome 50% to 60%	Low	
Anticentromere	Scleroderma 10% to 15%, CREST 50% to 90%, Raynaud's disease 10% to 30%	High	Scleroderma or a closely related disease such as CREST or Raynaud's disease, >95%
Anti-Scl_{70}	Scleroderma 15% to 20%	High	Scleroderma >95%
Anti-PM-Scl	Polymyositis 10%	Unknown	? Polymyositis
Anti-Jo_1	Polymyositis 30%, dermatomyositis <10%	Unknown	? Myositis

CREST=calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia; MCTD=mixed connective tissue disease; RA=rheumatoid arthritis; SLE=systemic lupus erythematosus

TABLE 4.—*Indications for Doing Tests for Antinuclear Antibodies*

Test	*Indication*	*Usefulness*
Fluorescent antinuclear antibody (FANA)	Patient with possible SLE, drug-induced lupus or MCTD	A negative test virtually excludes these diseases A positive antinuclear antibody test, while nonspecific, increases the posttest probability of disease
Anti-nDNA*	Patient with features of SLE and a positive FANA	A positive test (high titer) substantially increases the posttest probability that the patient has SLE
Anti-Sm	Patient with features of SLE and a positive speckled FANA test pattern	A positive test substantially increases the posttest probability that the patient has SLE
Anti-Ro (anti-SSA)	Woman of child-bearing age with a known connective tissue disease	Counseling, a positive test associated with a small but real risk of neonatal SLE and congenital heart block
	Patient with a negative FANA but a high pretest probability of SLE	A positive test increases the posttest probability that the patient has SLE
Anti-nRNP	Patient with possible MCTD	A negative test essentially excludes the diagnosis of MCTD A positive test in high titer, while nonspecific, increases the posttest probability that the patient has MCTD

MCTD=mixed connective tissue disease, SLE=systemic lupus erythematosus

*The titer of anti-nDNA is used by some specialists to monitor the activity of SLE; clinical features and other laboratory tests, however, are of equal or greater usefulness.

disease activity, making this a potentially useful index to monitor response to therapy. In a given patient, however, other clinical and laboratory features such as hematologic values, a urinalysis, serum complement levels and the like may be more helpful than the level of antibodies to nDNA.

Anti-Sm and Anti-nRNP Antibodies

The Sm (Smith) and nRNP antigens are closely related immunologically and are composed of protein and small RNA species. The presence of antibodies to Sm, like antibodies to nDNA, counts as a criterion for an "immunologic disorder" in the revised American Rheumatism Association criteria for lupus erythematosus. While the presence of antibodies to nRNP is not specific for patients with a mixed connective tissue disorder, the exclusive presence of a high titer of antibody to nRNP without other antinuclear antibodies appears to be unique to patients with this disorder. The absence of antibodies to nRNP virtually excludes the diagnosis of the disease.

Antibodies to Histone

The presence of antibodies to histone is associated with several rheumatic diseases including drug-induced lupus erythematosus, rheumatoid arthritis and systemic lupus. In a patient with suspected drug-induced lupus, measuring the level of antihistone antibodies adds little diagnostic value to a positive FANA test.

Antibodies to the Centromere Antigen

Antibodies to the centromere antigen can usually be detected only in rapidly dividing tissue culture cell lines that include numerous mitotic figures. Occasionally they can be detected using the HEp-2 substrate. Although early studies suggested that the presence of antibodies to the centromere was specific for the CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia) variant of scleroderma, further studies have shown that the presence of anticentromere antibodies is not specific for this syndrome. The exact diagnostic and prognostic significance of anticentromere antibodies remains to be defined.

Antibodies to the Ro (SSA) Antigen

The Ro antigen (identical to SSA, which stands for Sjögren's syndrome A antigen) is a protein-RNA complex that can be found both in the nucleus and in the cytoplasm of HEp-2 cells. It cannot be detected on mouse, kidney or liver tissue sections. As noted in Table 3, the presence of antibodies to Ro is not specific for any disease. The real significance of anti-Ro antibodies rests with certain disease associations:

- Anti-Ro positivity in a woman with a connective tissue disease is associated with a small but real risk of neonatal systemic lupus erythematosus and congenital heart block if the patient becomes pregnant.
- Patients with "subacute cutaneous systemic lupus erythematosus," who frequently have a negative FANA test, usually have detectable anti-Ro antibodies.
- Patients with Sjögren's syndrome who have anti-Ro antibodies appear to have more aggressive disease, particularly vasculitis.
- Anti-Ro antibodies are commonly detected in patients who have the lupuslike syndrome associated with a deficiency of the second component of complement.

Thus, the presence of anti-Ro antibodies may be helpful diagnostically or prognostically in a select few patients.

Antibodies to Other Nuclear Antigens

Many different nuclear antigens including anti-La (identical to anti-SSB), anti-Scl_{70}, anti-PM-Scl and anti-Jo_1 have been well characterized. The clinical value of finding elevated levels of antibodies to one of these nuclear antigens in a given patient has not been adequately defined.

Conclusion

The indications for doing specific antinuclear antibody tests are summarized in Table 4. Patients possibly having systemic lupus, drug-induced lupus or a mixed connective tissue disorder (pretest probability of disease ranging between 10% and 90%) should be tested for the presence of antinuclear antibodies. A negative FANA test is very useful in excluding these possible diagnoses. With the possible exception of a rim pattern FANA test, a positive test is nonspecific. Tests for antibodies to nDNA and the Sm antigen may be diagnostically useful when there is a moderate probability of systemic lupus erythematosus. The absence of antibodies to nRNP is helpful in excluding the diagnosis of mixed connective tissue disorder. Antibodies to Ro may be useful in a number of rather rare clinical situations.

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Soviet Health Care System

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Reliable information about the system of health care pertaining to the average Soviet citizen is difficult to come by. The health care offered important officials, artists and foreigners who become ill is at a much more sophisticated level than that available to the general Soviet community. Anecdotal reports[1-5] depict the personal encounters of Western travelers with the health care system and reflect the preferential treatment given sick foreigners. Some information about the Russian standard of medical care has been gleaned from interviews of Soviet physicians by Western lay correspondents[1-4,6] and by Western health care professionals.[7-11]

This overview of the Soviet health care system resulted from observations made during a recent ten-week stay in Leningrad. The information is taken from personal interviews with physicians and medical students, some of which were conducted on an official basis and others during candid private discussions. Likewise, visits to polyclinics were made on official tours, but also unofficially with Russian friends. This involved accompanying Soviet citizens during spontaneous visits to their local polyclinic, observing first hand the interaction of physicians and patients and touring the facility. In addition, Russian lay people related their personal experiences with the health care system. Between the official accounts, which strove to present the system in the best possible light, and the unofficial information, which pointed out some inadequacies as well as successes, a fairly comprehensive picture emerged with surprisingly few contradictions.

The information presented here pertains only to the medical establishment in Leningrad. The level of sophistication in providing health care may vary according to geographic location in the Soviet Union, as for example rural areas, or Asian Russia.[12] Because Leningrad is the Soviet Union's second largest city, however, it may be safe to assume that health care there represents the Soviet's best efforts.

Medical Education

Every Soviet citizen is required to complete ten years of primary and secondary education beginning at age 6 or 7. Higher education can then be pursued either in a university, specialized institute or a trade school. Following the tenth grade, Soviets begin medical training in special medical institutes. Unlike their American counterparts, Soviet medical schools do not function within a university setting, but rather are individual technical schools. Their mandate is solely to train medical practitioners, and this keeps the medical institutes separate from the more elite Soviet research establishment. There is an entirely different school of medicine for those destined to become pediatricians.

Entrance to a medical institute is difficult. There are competitive examinations involving oral tests in biology and physics (chemistry used to be included). Written essays are required concerning 19th century literature and Soviet literature and a "creative" essay indicative of an applicant's political and patriotic proclivities. According to several young medical students, the system is not without its bias. For example, Jews have a difficult time gaining entrance to a medical institute. Their oral examinations are much more difficult, and on occasion they are given insoluble physics problems to solve. On the other hand, other persons with money or influence seem to have less trouble gaining admission to a medical institute. Some students with poor grades who initially were refused admission can, by using influence, obtain a job for a year or two in a factory. Remedial courses are offered to workers, and after a year or two, that person can be admitted to the medical institute without taking any more competitive examinations. A route less sure than a factory job is to work in a hospital as an orderly. This is a comparatively undesirable job and usually does not eventuate in a place at an institute.

The course of study in both the medical and pediatric institutes is six years. The curriculum is with few exceptions similar to the courses offered in American medical schools. College chemistry, biology and genetics and a language (usually Latin) are offered in the first two years, as are courses in the history and philosophy of the Communist party. Students are taught in the hospitals and polyclinics from the first year, where they learn to interview patients. They are also expected to do janitorial and maintenance work. During the later years students become involved with more formal clinical rotations. Each clinical rotation is preceded by didactic lessons in that discipline.

At the end of six years the students graduate from the medical institute. They spend the following year as interns in residence at a hospital. Medical training is over at the completion of internship, and physicians are obligated to serve another two to three years for the State. Following this, they begin a more permanent medical practice either in a hospital, polyclinic or on an ambulance.

In the Soviet Union each ambulance has a physician on board. Patients too ill to go to a polyclinic can dial an emergency telephone number. An ambulance is dispatched, sometimes after a several-hour wait, and a physician, in effect, makes a house call. He or she can assess the situation and either treat on site or transport the patient to a hospital. Ambulance equipment varies, but usually includes a

(Friedenberg DS: Soviet health care system. West J Med 1987 Aug; 147:214-217)

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manual respirator and a defibrillator. The physician is generally unfamiliar with the patient's history, and if the patient is transported to a hospital, further care is assumed by the hospital physicians.

Specialty training in the Soviet Union is relatively uncommon and is very different from the American system. There are no specialty boards in the same sense as ours, and there is no specified time or competency requirement. Quite simply, one goes to great lengths to secure a position in a specialized polyclinic or hospital corresponding to the desired specialty. These positions can be impossible to obtain, and often success depends on a physician's proper connections or money. Surgical specialty training is an example. Any physician can do simpler surgical procedures such as an appendectomy or herniorrhaphy. More complicated procedures are done at specialized regional centers and physicians desiring surgical expertise need to find positions at those centers. At the end of 5, 10 and 15 years, respectively, those with more advanced specialty training can take an examination, which certifies them to a successively higher category of expertise. These categories correspond to increments in salary. Actual training time in specialty fields such as cardiology averages three to six months.

Continuing medical education is an area where official and unofficial accounts differ. Officially, continuing medical education courses are given anywhere from once a month to, according to one polyclinic director, four months out of the year. Unofficially, some physicians interviewed admitted attending only one lecture per month at best, and the value of those discussions is dubious. Medical journals exist, but physicians do not generally subscribe to them. Journals are kept in the libraries, but few physicians go there to read them. The apathy with which many physicians approach their work appears to be multifactorial. Medicine is a low status profession in the Soviet Union. The average physician's monthly income is about 145 rubles ($210), whereas the overall average per capita income in the Soviet Union is 190 rubles ($275) per month. A physician's pay is the same regardless of the number of patients treated. Medical practice is felt by many to be very routine, nonstimulating and unfulfilling. The work incentive therefore is low, and overall job satisfaction tends to be low.

In the upper echelon of the medical establishment, a professor can earn as much as 500 rubles per month, with added income at inflated rates from private consultations. Private practice is illegal but is widely engaged in by the highly sought-after medical elite. The authorities rarely, if ever, prosecute physicians for accepting private fees; in fact, offering physicians bribes or special favors is a mechanism frequently used by Russians to ensure attentive service.

Polyclinics

The cornerstone of the Soviet health care system is the polyclinic. This is an outpatient facility located in each neighborhood. Services are available with no appointment necessary, and it is always free of charge. There are separate polyclinics for pediatric and adult medicine. The physicians are mostly general practitioners who handle a wide variety of general medical and surgical problems. Patients usually see the same physician at each visit, although they have little choice over which physician they see. The task of a polyclinic physician is to treat simple problems and to do diagnostic workups on an outpatient basis whenever possible.

A major function of the polyclinics is to assess the ability to work. Patients with major illnesses can be placed on a pension if they are so certified by a physician. Polyclinic physicians routinely grant paid work excuses for anywhere from three days for a minor illness to four months for more serious maladies. Those suffering from tuberculosis receive a ten-month paid work excuse. The mother of a child younger than 14 years who becomes ill is granted a seven-day work excuse, ten days if she is a single parent.

Each polyclinic has a simple laboratory wherein a physician can do microscopic urinalyses, measure hematocrits by sedimentation, study peripheral blood smears and examine specimens of stool, sputum and gastric secretions and vaginal smears. Chemical determinations such as electrolytes can be done only at special regional laboratories, and such tests are rarely ordered. Almost every polyclinic has x-ray equipment, and each year every Soviet citizen is supposed to receive a fluoroscopic chest x-ray examination to screen for tuberculosis and lung cancer. Some Soviet citizens privately admitted to missing many of these yearly examinations. An electrocardiogram is not done on a routine basis and is ordered only if clinically indicated or if a patient is engaged in what is perceived to be a stressful occupation.

When appropriate, polyclinic physicians can refer patients to specialized regional polyclinics for evaluation for particular illnesses. It is in these centers that outpatients can see specialists, and special diagnostic tests such as gastrointestinal series, intravenous pyelography, mammography and M-mode ultrasonography can be done. Angiography is rarely done because of the lack of equipment and expertise in this area. According to the physicians interviewed, computed tomographic and magnetic resonance imaging scanners are virtually nonexistent in the Soviet Union, even in the major medical centers. This is the case at the N.N. Petrov Oncologic Institute in Leningrad, one of the two largest cancer treatment and research centers in the Soviet Union.

Public Health and Preventive Medicine

An important function of the Soviet health care system is preventive medicine. Frequent visits to a polyclinic begin during the neonatal and infant periods. Children are routinely vaccinated against diphtheria, pertussis, tetanus, polio and mumps. They also receive a bacille Calmette-Guérin vaccine, and conversion to positive on a Mantoux test is considered evidence of protection against tuberculosis. Children are sent to "Pioneer" summer camp each year to be exposed to the sunshine and fresh air of the countryside and to be away from what are considered the unhealthy influences of the city. They are examined in a polyclinic when they return from camp, just before starting school.

There are many different public health problems in the Soviet Union. The diet is rich in saturated fats; Russians enjoy fried foods, butter, eggs, cheese and red meat when it is available. Produce is very expensive and difficult to obtain during the winter months. Starches such as bread and potatoes provide a high-caloric density, and obesity is prevalent. Pollution control is grossly inadequate, although the

government is trying to move major industrial plants outside city limits. Despite government claims to the contrary, air and water pollution is obvious. Since the accident at the nuclear reactor at Chernobyl, radioactive contamination of water and food is a potential problem, the magnitude of which is difficult to assess.

Alcoholism is rampant in the Soviet Union, and under the new leadership of Mikhail Gorbachev, a major campaign has been launched in an attempt to control the problem. The sale of alcohol has been limited to specific hours. The price of vodka has skyrocketed, and the lines in stores that sell vodka are formidable even by Soviet standards. Penalties for public drunkenness are severe and may at the very least involve a beating by police. A major internal propaganda campaign against alcoholism is apparent. Still, alcohol rehabilitation programs involving detoxification and counseling as we know them in the West do not yet exist.

Cigarette smoking is widely practiced in the Soviet Union. A health warning is printed on each package of cigarettes, but a grass roots sentiment that it is important or desirable to stop smoking is not evident.

The health care system attempts to have a favorable impact in the workplace. Occupational medicine has brought routine screening examinations to workers at the factories. Food handlers and those working in the bath houses, for example, are screened for enteric and vaginal infections. Those with high-level dust exposure such as factory workers or librarians receive routine chest examinations. As mentioned previously, electrocardiograms are done routinely in those considered to be engaged in stressful occupations.

Therapeutics

The Soviet Union has a rudimentary pharmaceutical industry. Consequently, most of their drugs are imported, usually from other Eastern Bloc nations or from Western Europe, particularly France. Medications can be purchased at a surprisingly low price from the neighborhood *apteka*, or pharmacy, on a nonprescription basis. Medicines are not compounded by a pharmacist, but rather are dispensed by a nurse. Many drugs are in short supply, and it is sometimes necessary to search the city to locate an *apteka* that has the desired medication in stock. Very young children receive medications directly from the polyclinics free of charge.

In addition to the more familiar, a few unconventional therapeutic modalities are offered at polyclinics. One of the more unusual is called electrical therapy. A power supply unit delivers an electrostatic charge to a glass probe. The probe is passed over the diseased part of a patient's body, whereupon a series of electrostatic sparks is administered. The glass probes can be interchanged so that the electrical therapy can be delivered directly into body orifices or topically over skin surfaces. The treatment is considered to be a type of physical therapy, but some physicians privately admitted they have reservations as to its efficacy.

Another type of electrical therapy appears to be similar to the transepidermal nerve stimulator. Electrodes are applied to a patient's skin over a painful area, and an electric current is applied for purposes of analgesia. These units are large and are not battery powered; they are not intended for ambulatory use.

Ultraviolet light therapy is commonly administered to children. It is felt that the poor climate in Leningrad does not afford children enough exposure to sunlight, and this can lead to vitamin D deficiency with subsequent rickets. Milk is not fortified with vitamin D, and vitamin D_3 supplements are apparently not available. The actual incidence of rickets in Leningrad could not be assessed. Acupuncture is popular in the Soviet Union and is a widely practiced treatment modality in the polyclinics.

Glass syringes and reusable needles are the rule in Soviet polyclinics. Examining gloves, urinary catheters and intravenous tubing are also reused. Intravenous solutions are freshly made up and autoclaved in glass bottles, and metal needles are used instead of plastic intravenous catheters. Intravenous infusions, including chemotherapeutic agents, are mixed and administered by nurses rather than physicians or pharmacists.

Emergency rooms as such do not exist in the Soviet Union. During the daytime patients either report to their neighborhood polyclinic or call an ambulance. Several polyclinics in each district remain open 24 hours a day to treat emergencies or mild trauma. Emergency surgical procedures are usually handled expeditiously. Elective operations involve a waiting period; the more complex procedures are done only at regional centers, and these places tend to have longer waiting lists than do the local hospitals, which are equipped to do simpler or more common procedures. Very advanced operations that use high technology, particularly vascular procedures such as coronary artery bypass grafting, carotid endarterectomy and angioplasty, appear to be virtually nonexistent in the Soviet Union for the average citizen. Instead, a large emphasis is placed on physical therapy and rehabilitation following myocardial infarction or stroke.

Many Russian citizens interviewed related that they have little confidence in polyclinic physicians. The prime motivation to visit a polyclinic is often only to obtain a work excuse. This attitude partially stems from a widely held belief that anything one can get for free cannot be good. Adherents to this philosophy usually pay a physician privately. Many people have serious doubts altogether about the ability of the orthodox system of medicine, with its reliance on drug therapy, to treat disease. Consequently, alternative approaches to health care have become popular. Homeopathy is one such approach, and a homeopathic hospital operating on a fee-for-service basis flourishes in Leningrad. Chiropractic has not caught on yet, but herbal medicine has. This is referred to as *trava*, which literally means "grass." Popular folklore concerning grasses, herbs, mushrooms, roots and other natural products with reputed medicinal properties is handed down either by elderly women from the countryside who are knowledgeable about such matters or more recently in books and periodicals. *Trava* in its various forms can be gathered in the forests or countryside, and some are available even in an *apteka*.

Ironically, in a purportedly atheistic country such as the Soviet Union, faith healing and "psychic healing" have a number of proponents, particularly in the more rural areas.

Conclusion

Soviet health care would have to be considered somewhat behind Western standards. The advanced medical

technology that has arisen in the West in recent decades has never become a part of the Soviet system. More specifically, medical intensive care units, hemodynamic monitoring, vascular and microsurgical techniques and computerized diagnostic modalities—to name a few—have not become a routine part of Soviet medical care. Because of this, ordinary physicians have less to cope with in terms of the proper use of these systems, and one year of postgraduate medical training appears to suffice. The situation is reminiscent of that in the United States after World War II before the age of specialization.

Soviet medicine is best assessed by comparing it with its past, and not by comparing it with present-day Western standards of care. In this regard, the Russians are proud of its steady improvement. The emphasis in the Soviet Union is on providing universally available free medical care, and, at least in Leningrad, this appears to have been achieved. To be sure, the health care system seems to suffer from many of the same ills as the rest of Soviet society, such as low work incentive, poor productivity, corruption and elitism. But overall, the Soviet physicians interviewed seemed to be pleased with the quality of care provided, and most felt that the system is adequate to meet the needs of their people.

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Special Article

Consent and Confidentiality Laws for Minors in the Western United States

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Minors' rights in health care are creating confusion for many health care professionals. Laws vary from state to state and are often ambiguous. State legislatures in many states have attempted to modify consent laws for minors to increase their access to health care.

(Neinstein LS: Consent and confidentiality laws for minors in the western United States. West J Med 1987 Aug; 147:218-224)

Minors' health care rights are confusing to physicians. The ambiguity of the laws, the variations from state to state and societal ambivalence add to this confusion. Inherent conflicts between the needs of teens and their parents may create ethical dilemmas for health professionals.

The requirement of parental consent for minors' health care stems from the common-law principle that touching an unconsenting person constitutes a battery. While obtaining consent from an adult is usually not a major problem, traditionally children have been considered incapable of giving consent. Without parental consent, a physician attempting to provide health care would potentially be liable for a battery charge.[1,2] Legislatures over the years, however, have created exceptions. These have usually been written realizing that while parental involvement is desirable, many adolescents might avoid medical care rather than risk parental involvement. The problem areas usually involve sensitive issues such as sexually transmitted diseases. In this article I will clarify current law regarding health rights of teenagers in the western United States, including rights of confidentiality, record privacy rights and payment liability.

Consent

While consent laws vary between states there is legal support, even in the absence of specific laws, for the "mature minor rule."[3,4] This doctrine suggests that minors can consent to medical treatment when they are mature enough to give informed consent and if treatment is to their benefit. This doctrine confers probable, not absolute, immunity from liability. There are no reported decisions in the past 25 years in which a parent recovered damages for treatment of a child older than 15 years without parental consent.[5] The mature minor doctrine is *not* a substitute for consent statutes. If the statutes are unclear and the mature minor doctrine is used, legal counsel should be obtained. The American Academy of Pediatrics has the following guidelines[6]:

- Minors make most of the decisions about their daily affairs.
- Minors enjoy substantial independence in their comings and goings from home.
- Even though supported by their parents in major matters, minors earn their personal expense money and manage most of their financial matters.
- Minors initiate their own medical appointments, come by themselves, state their own needs and seem able to follow through with recommendations.
- They appear to understand both the risks and the benefits of proposed treatment and thereby are able to give an informed consent.
- They are unable to readily communicate with their parents.

Confidentiality

Confidentiality of minors' care is a separate and often difficult issue. If minors can give consent for their own care, should or can a provider inform the parents of a minor or must or can the health care provider keep the information confidential? If medical records are requested, who must consent to their release? While most states do not address these issues, Ellen Covner Weiss, General Council of Children's Hospital Medical Center in Boston, has written some excellent guidelines (unpublished). These represent her guidelines and not established law, nor should they be substituted for legal consultation for individual cases. Her recommendations include the following:

- Regardless of whether a minor is deemed mature or emancipated, if the patient's condition is life-threatening to self or others, this information probably should be disclosed.
- For a patient whose condition is not life-threatening to self or others:
  1. If the patient is a mature and emancipated minor (many legal authorities would base this on what conditions the minor is legally able to consent for), do not disclose unless the patient consents or the information is sought by court order and there is no prohibition against such disclosure.
  2. If the patient is not a mature or emancipated minor, do not disclose unless a legal guardian consents or the information is sought by court order and there is no law against disclosure.

Payment

Usually there is no problem regarding financial liability when a parent gives consent for a minor. The problem arises when minors give consent for their care without parental knowledge or agreement. This can be a particular problem for

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ABBREVIATIONS USED IN TEXT

ARS = Arizona Revised Statutes
CCC = California Civil Code
CRS = Colorado Revised Statutes
ICA = Idaho Codes Annotated
MRCA = Montana Revised Codes Annotated
NMSA = New Mexico Statutes Annotated
NRS = Nevada Revised Statutes
ORS = Oregon Revised Statutes
RCW = Revised Code of Washington
RCWA = Revised Code of Washington Annotated
UCA = Utah Codes Annotated
WSA = Wyoming Statutes Annotated

a physician relying on the parents' insurance for reimbursement. Where the issue is codified, I will summarize it.

Statutory Rape

While all the states have some definition of illegal sexual activity for minors younger than 18 years, the practice of enforcing this law varies from the letter of the law. Because of the varying enforcement of these statutes, practitioners are advised to contact the local police department or district attorney if a question arises. Often a critical issue is whether the "illegal" conduct comes under child abuse reporting laws.

Abortion

Although at present abortion is legal for minors under Supreme Court rulings, the following western states have parental notification laws[7,8]:

Arizona

The parental notification law provides for a judicial bypass procedure and, if a minor is found to be mature, notification is waived.

Idaho and Montana

The parental notification law does not contain a judicial bypass procedure (and therefore its constitutionality is questionable).

Nevada

The parental notification law contains no judicial bypass procedure and is currently under court injunction.

Utah

The parental notification law does not contain any judicial bypass. This notice was upheld by the Supreme Court but only as to the class of minors represented by the plaintiff—immature minors living at home who had no reasons indicating that their parents should not be notified.

Contraception

The Supreme Court has ruled that contraception must be made available to minors and that states may not prohibit such access. While many states have statutes recognizing a minor's right to obtain contraceptives, others have either no statutes (Arizona, Nevada, Washington, Wyoming) or have a general medical consent law (Idaho, New Mexico).

Arizona

Adolescents may consent for any health care, excluding sterilization, if they are the following[9]:

- Older than 18 years—must be legally competent—Arizona Revised Statutes (ARS) 1-215, 1978 to 1979.
- Married, emancipated or a minor in the military—ARS 44-132.

No Arizona statute defines emancipation. This is a question of fact that must be proved. Parental intent to relinquish control is one key factor.[10]

A teenaged mother has the right to consent for her child's medical care but not her own medical care, unless she is emancipated.

Specific Circumstances

Teens may self-consent for the following:

1. *Emergency care.* A surgical procedure is permissible without parental consent if an emergency exists and it is necessary for the treatment of a serious disease, injury or drug abuse—ARS 36-2271.
2. *Venereal disease.* Any-aged minor may consent for the examination and treatment of venereal disease—ARS 44-132.01.
3. *Drug or narcotic abuse.* Minors 12 years and older can consent to their own care for treatment of drug problems. Any minor 12 years or older found to be under the influence of a dangerous drug may be considered an emergency, and such minor is to be regarded as having consented to hospital or medical care—ARS 44-133.01.
4. *Sexual assault.* A minor 12 years or older may consent to medical care if a legal guardian cannot be found and evidence collection is important—ARS 13-1413.
5. *Mental health treatment.* No specific statutes or judicial decisions address this, but counseling with regards to venereal disease and drug abuse would be allowed by previous statutes. Psychiatric care would be considered medical care and would require parental consent. Legal opinion on this issue, however, would suggest that mature minors in a crisis could consent to therapeutic counseling without parental consent.
6. *Blood donation.* Anyone aged 18 or older may consent—ARS 44-134.

Arizona law does not specifically grant minors the right to consent for contraception or pregnancy-related care. Arizona has no specific laws on confidentiality for minors.

Payment

Sexual assault. Parents are not liable in Arizona for payment for any services pursuant to the sexual assault consent section—ARS 13-1413. Payment liability regarding other statutes is not discussed.

California

In California teens may consent for their own care[11,12] if they are the following:

- Older than 18 years, the age of majority—California Civil Code (CCC) 25.1.
- Married minors, considered majors—CCC 25.6.
- Minors in the armed services, considered majors—CCC 25.7.
- Self-sufficient minors—CCC 34.6. A "self-sufficient minor" is one who is 15 years or older, living separate from parents with or without consent, regardless of duration and managing own financial affairs, regardless of source of income. This group of minors may consent only for their own health care.
- Emancipated by a declaration of emancipation pursuant to CCC 64 by the superior court of their county of residence. The adolescent must be 14 years of age, must be living apart from parents or legal guardian with consent or acqui-

escence, must be managing his or her own financial affairs and the source of income must be legal—CCC 64.

Specific Circumstances

1. *Emergency medical care.* A physician is not liable if providing medical care to someone who is unable to give consent and, due to a life-threatening condition, there is insufficient time to contact the responsible person or legal guardian—Business and Professions Code 2397(a)(3).
2. *Venereal disease.* Minors aged 12 years and older may consent for hospital, medical and surgical care of contagious, infectious or communicable diseases that are required by law to be reported to a local health officer—CCC 34.7—or a sexually transmitted disease as determined by the State Director of Health Services—17 Administration Code Section 5151(a). There are 5 sexually transmitted diseases and 50 contagious diseases that are reportable to local health officers. There are 11 sexually transmitted diseases for which the State Director of Health Services has determined that minors aged 12 and older may also give independent consent.
3. *Drug or alcohol problems.* Minors 12 years or older may give consent for medical care, including admission to hospital and counseling, regarding the diagnosis and treatment of a drug- or alcohol-related problem—CCC 34.10.
4. *Alleged rape.* A minor 12 years or older may consent to hospital, medical and surgical care of such a condition—CCC 34.8.
5. *Alleged sexual assault.* A minor may consent to hospital, medical and surgical care for diagnosis and treatment of such a condition—CCC 34.9.
6. *Contraception and pregnancy-related care.* Unmarried minors regardless of age may consent to hospital, medical and surgical care related to the prevention and treatment of pregnancy—CCC 34.5.
7. *Mental health treatment.* A minor 12 years or older who is mature enough to participate in mental health treatment and would present a danger to self or others or is an alleged victim of incest or child abuse may consent to outpatient services—CCC 25.9. This does not include electroshock therapy, psychotherapy or psychotropic drugs.
8. *Blood donations.* A minor 17 years or older may consent to donate blood without compensation—CCC 25.5.
9. *Parenting minors.* Minors who are parents can consent for medical care for their children.

All of the consent laws include inpatient hospital care, except mental health treatment. This includes the minors' ability to be discharged to their own care without the presence of guardian if the admission was based on their own consent—22 California Administrative Code 70717(q).[11]

A minor may give independent consent for any area of medical care if the teen is sufficiently mature to give informed consent (Ballard versus Anderson).[12] This likely involves the teen's ability to understand the information given by a physician and to make a decision between alternatives presented.[12]

A minor's right to refuse treatment is not clear under California law. English concludes that minors probably have the right to refuse care, particularly reproductive health care, in areas where the minors have the right to consent.[12] This is based on California Administrative Code 70707(b)(6), United States constitutional law protecting the right of privacy, including the right to refuse treatment, and US constitutional law extending the rights of privacy to minors with respect to abortion and contraception. This concept has not been tested in California, and providers are advised to seek legal counsel if this issue arises.

Confidentiality

In California, health care professionals should inform parents of ongoing care if:

- A minor is younger than 18 years and there are no special circumstances, or it is an emergency medical situation.
- In situations of sexual assault, unless the parents are the abusers—CCC 34.9.
- In mental health treatment situations, unless such involvement would be inappropriate—CCC 25.9. The provider should note in the record when the parents were contacted, whether the attempt was successful or the reason why it was inappropriate to contact the parents.
- In persons receiving drug or alcohol abuse counseling, unless such involvement would be inappropriate—CCC 34.10.
- If a minor has consented as a self-sufficient minor under CCC 34.6, then the health professional may advise the parents of the treatment, whether or not the minor agrees that the parents be contacted—CCC 34.6.

Ethics would suggest that a minor be informed of such contact first. Legal opinion is against informing parents in the following circumstances:

- If a minor is married, legally emancipated or in the armed forces.
- If a minor is able to give independent consent and has asserted the physician-patient privilege of confidential communication—Evidence Code Section 994. Child abuse reporting obligations override this.
- If confidential communications between a psychotherapist and a minor exist—Evidence Code Section 1014.5. Exceptions to this privilege include situations involving minors younger than age 16 who are victims of a crime when the psychotherapist determines that it is in the best interest of the minor to disclose—Evidence Code Section 1027—and situations governed by child abuse reporting laws. A therapist may also disclose if the therapist feels a minor is a threat to self or others—Evidence Code 1024. A minor also has the right to control disclosure of confidential medical information for which the minor has the right to give consent—CCC 56.11.

Access to Health Records

Parents or guardians have the right to access the medical records of a minor unless it is a situation in which a minor has the right to inspect his or her own records, or where a health professional feels it is detrimental to the provider's relationship with the minor—Health and Safety Code 25252(a), 25253(a).

If a minor is authorized to consent to medical treatment, the minor has the right to access the records—Health and Safety Code 25252(a).

Payment

Parents are not liable for payment nor can payment be requested of parents of self-consenting minors for care in the following areas:

- Any care for which minors give independent consent—Welfare and Institutions Code 14010.
- Mental health care if the parents are not participants—CCC 25.9.
- Drug or alcohol counseling and treatment if the parents are not participants in the program—CCC 34.10.

Parents are not liable for payment for any care for which minors are legally authorized to consent, unless the parents have agreed to pay.

Self-consenting minors incur financial liability for services, but they may qualify for MediCal (California's medicaid) for services to which they may legally consent. Collecting payments may be a problem unless a minor is covered by MediCal or an insurance plan providing confidential handling of minors' claims.

Colorado

In Colorado teens may self-consent for health care[13] if they are

- Older than 18 years, age of majority—Colorado Revised Statutes (CRS) 13-22-101.
- Married minors—CRS 13-22-103.
- Minors in the armed services—Army Regulations 40-3.
- An emancipated minor—CRS 13-22-103. This is defined as a minor 15 years old or older living separate from parents or legal guardians with or without consent and managing his or her own financial affairs, regardless of the source of income.

Specific Circumstances

1. *Venereal disease.* Any minor may consent to examination for or treatment of venereal disease—CRS 25-4-402.
2. *Drug abuse.* Any minor may consent to medical care for addiction to the use of drugs—CRS 13-22-102.
3. *Sexual assault.* Minors may consent to examination, evidence collection and treatment. Before examining, a physician should make a reasonable effort to notify parents—CRS 13-22-106, 19-10-106, 108.
4. *Contraception.* Any minor may be furnished birth control procedures, supplies and information who requests and is in need of such services. This also includes any pregnant minor, married minor or a minor referred by a physician, member of the clergy, family planning clinic, school or any agency of the state—CRS 13-22-105. The statute provides that medically acceptable contraceptive procedures, supplies and information be readily available to every person regardless of sex, race, age, income, number of children, marital status, citizenship or motive—CRS 66-32-2.
5. *Blood donation.* Anyone older than 18 years can consent to donate blood—CRS 13-32-104.

Confidentiality

Physicians do not need to inform parents of treatment of self-consenting minors for venereal diseases—CRS 25-4-402—or drug abuse—CRS 13-22-102. Physicians, however, shall attempt to contact parents in cases of sexual assault—CRS 13-22-106.

Payment

Parents are not liable for payment if a minor consents as an emancipated or married minor, unless the parents agree to liability—CRS 13-22-103.

Idaho

In Idaho teenagers may consent for their own health care[14] if they are older than age 18, the age of majority—Idaho Codes Annotated (ICA) 32-101.

Specific Circumstances

1. *Emergency care.* An attending physician or dentist may authorize care whenever there is no person readily available and willing to give consent and, in the judgment of the attending physician or dentist, the case presents a medical emergency—ICA 39-4303.
2. *Venereal disease.* Any minor aged 14 or older may consent to hospital, medical or surgical care related to the examination for or treatment of any infectious, contagious or communicable disease—ICA 39-3801.
3. *Drug abuse.* Any minor aged 16 or older may consent to examination or treatment for drug dependency—ICA 37-3102.
4. *Contraception.* A physician or licensed health care provider acting at his or her discretion or medical order may provide examination, prescriptions, devices and informational materials regarding preventing conception to any person requesting the same who, in the good faith judgment of the provider, is sufficiently intelligent and mature to understand the nature and significance thereof—ICA 18-603.
5. *Mental health hospital admission.* Any "emancipated minor" (a person between ages 14 and 18 who has been married or whose circumstances indicate that the parent-child relationship has been renounced) may consent to admission to mental hospital—ICA 66-317, 318.

Confidentiality and Payment

There are no specific laws regarding confidentiality or payment regarding minors in the Idaho statutes.

Montana

In Montana teens may self-consent for health care[15] if they are

- Older than age 18, the age of majority—Montana Revised Codes Annotated (MRCA) 41-1-101.
- A married minor, or a minor who has a child or graduated high school—MRCA 41-1-402.
- An emancipated minor—MRCA 41-1-402. This includes a minor who has separated from parents or legal guardian for whatever reason and is self-supporting by whatever means.

Specific Circumstances

1. *Emergency care.* Any minor may consent to medical and surgical care, including transfusions, without which the minor's health care would be jeopardized—MRCA 41-1-402.
2. *Venereal disease.* Any minor may consent to treatment of any reportable communicable disease including venereal disease—MRCA 41-1-402.
3. *Drug and substance abuse.* Any minor may consent to treatment of drug or substance abuse—MRCA 41-1-402.
4. *Pregnancy.* Any minor may consent to the prevention, diagnosis and treatment of a pregnancy—MRCA 41-1-402.
5. *Mental health.* A minor may consent to counseling when, in the opinion of a physician or psychologist, the need is urgent (danger to life, safety or property of minor or of

other persons) and the consent of a guardian cannot be obtained—MRCA 41-1-406.

If a minor consents under conditions 2 through 4 above, the provider is obligated to counsel the teen or refer the teen for counseling—MRCA 41-1-402.

No health care professional may be compelled against his or her better judgment to treat a minor on the minor's own consent—MRCA 41-1-407.

Confidentiality

Health care professionals shall notify parents as soon as practical if emergency care is rendered, except under conditions for which minors have the right to consent—MRCA 41-1-402. A treating physician may, but shall not be obligated, to inform the spouse or guardian of such a minor for circumstances in MRCA 41-1-402 (Emancipated Minor and Minor Self-Consent Rule) when severe complications are present or a major operation or admission to hospital is needed or failure to inform parents would seriously jeopardize the safety and health of the minor, siblings or public, to inform them would benefit the minor's physical and mental health or the hospital desires a third-party commitment to pay for services.

Payment

Parents shall not be liable for payment for services to a self-consenting minor, unless parents expressly agree to pay. Minors so consenting assume financial responsibility, except those who are proved unable to pay—MRCA 41-1-404.

Nevada

In Nevada teens may self-consent for health care[16] if they are

- Older than 18, the age of majority—Nevada Revised Statutes (NRS) 129.010.
- Married (a minor who is or has been married)—NRS 129.030.
- A minor who is a mother or who has borne a child—NRS 129.030.
- An emancipated minor—NRS 129.030—includes a minor who is living separate from a legal guardian, with or without consent, for at least four months.

Specific Circumstances

1. *Emergency care.* A minor may consent if at risk of a serious health hazard if care is not provided. The minor should be able to understand the nature and purpose of the proposed examination and treatment and its probable outcome—NRS 129.030.
2. *Venereal disease.* A minor may consent to examination for and treatment of any venereal disease—NRS 129.060.
3. *Drug abuse.* Any minor who is under the influence or is suspected of being under the influence of a controlled or dangerous substance may give consent or, if unable to do so, shall be deemed to consent to hospital, medical, surgical or health care treatment of drug abuse or a related illness—NRS 129.050.
4. *Contraception.* No state statutes deal with this issue. Currently family planning clinics are prescribing contraception with minor's consent and without parental consent.
5. *Blood donations.* A minor older than 17 years may consent to donate blood.

Confidentiality

A person treating a self-consenting minor under NRS 129.030—that is, a married or emancipated minor, a minor mother or in an emergency condition—shall attempt to communicate with the legal guardians and make a note of such efforts. If such efforts would jeopardize the treatment necessary to the minor's life or necessary to avoid a serious and immediate threat to a minor's health, such a person may omit such efforts and note the reasons for omission in the health record—NRS 129.030. Any physician treating a minor for drug abuse shall make every reasonable effort to report such treatment to the legal guardians within a reasonable time after treatment—NRS 129.050.

Payment

Parents are not liable for payment for services provided to self-consenting minors in the areas under NRS 129.030, unless the parents or legal guardians have consented to such health services.

New Mexico

In New Mexico, teens may consent to their own health care[17] if they are

- Older than 18, the age of majority—New Mexico Statutes Annotated (NMSA) 28-6-1.
- Married minors—NMSA 24-10-1.
- Minors in the armed forces—NMSA 28-6-4, 24-10-1.
- Emancipated minors—NMSA 28-6-5. The state code requires a court declaration. The minor must be 16 years or older, living separate and apart from the parents or guardian, managing his or her own financial affairs and the court finds it in the minor's best interest.

Specific Circumstances

1. *Emergency conditions.* In emergency cases, if parents cannot be located consent can be given by anyone standing in *locus parentis*—NMSA 24-10-2.
2. *Venereal disease.* Any person, regardless of age, may consent to venereal disease examination and treatment—NMSA 24-1-9.
3. *Drug abuse.* Any person, regardless of age, may consent to treatment of drug abuse—NMSA 26-2-14.
4. *Pregnancy.* Any person, regardless of age, has the capacity to consent to examination and diagnosis for pregnancy—NMSA 24-1-13.
5. *Contraception.* Family planning services should be readily accessible to all who want and need them—NMSA 24-8-3, 24-8-5.
6. *Mental health.* Any minor may consent to individual or group psychotherapy or other forms of verbal therapy that do not include any adversive stimuli or substantial deprivations. This does not include electroconvulsive therapy or psychotropic medications—NMSA 43-1-17.

Confidentiality

Drug abuse. Records of drug abuse treatment are confidential and cannot be discoverable in criminal prosecution—NMSA 26-2-14.

Payment

Drug abuse. Parents are not liable for payment if treatment was made without parental consent—NMSA 26-2-14.

Mental health. A parent shall be responsible for the cost of mental health services provided to the parent's minor child—NMSA 43-1-17.

Oregon

In Oregon teens may self-consent for health care[18] if they are

- Older than age 18, the age of majority—Oregon Revised Statutes (ORS) 109.510.
- A married minor—ORS 109.520. A married minor is considered a major.
- Older than age 15; any minor 15 years or older may consent to hospital care, medical or surgical diagnosis or treatment—ORS 109.640.

Specific Circumstances

1. *Venereal disease.* A minor may give consent for any surgical care related to the diagnosis and treatment of any venereal disease required by law or regulation to be reported to a local or state health office—ORS 109.610.
2. *Drug abuse.* Any person may voluntarily apply for admission to any treatment facility for drug or alcohol addiction—ORS 426.450.
3. *Contraception.* A physician can provide birth control information and services to any person without regard to age—ORS 109.640.
4. *Blood donations.* Any minor aged 16 or older can donate blood in a voluntary and noncompensatory program—ORS 109.670.

Confidentiality

Any hospital or physician may advise parents of care rendered under ORS 109.640 (contraceptive services and medical care for self-consenting minors older than 15) without the minor's consent—ORS 109.650. If a person is younger than 18, the legal guardians shall be notified of drug and alcohol admissions. Records of such admission shall not be revealed without the parents' consent other than to the parents of a minor—ORS 426.460.

Payment

Venereal disease. Parents are not liable for payment for self-consenting minors in this area if parents did not give consent—ORS 109.610.

Utah

In Utah teens may self-consent for health care[19] if they are

- Older than age 18, the age of majority—Utah Codes Annotated (UCA) 15-2-1.
- A married minor—UCA 15-2-1.
- Consent for a minor's care may be given by his or her spouse—UCA 78-14-5.

Specific Circumstances

1. *Venereal disease.* Any minor may consent for medical or hospital care for a suspected venereal disease—UCA 26-6-18.
2. *Pregnancy.* Any woman regardless of age can give consent for health care related to pregnancy and childbirth—UCA 78-14-5.
3. *Contraception.* No public funds may be used for contraception for unmarried minors without parental consent—UCA 76-7-321. Although the Utah Health Department, in using its own funds, can apply such requirements, it cannot apply such requirements in administering a federal grant.[20] Utah has a statute—UCA 76-7-325—requiring parental notification before providing contraceptives to minors. This section was ruled unconstitutional, however.[21]
4. *Blood donation.* A person 18 or older can consent to donate blood—UCA 15-2-5.

Confidentiality and Payment

There were no specific statutes found in the areas of confidentiality and payment regarding minors, except that treatment for sexual abuse can only be disclosed if a patient is a minor and it is in the best interests of the patient to disclose to parents—UCA 78-3C-4.

Washington

In Washington teens may self-consent for health care[22] if they are

- Older than age 18, the age of majority—Revised Code of Washington (RCW) 26.28.015.
- A married minor who is married to a person of full age—RCW 26.28.020.

Specific Circumstances

1. *Emergency conditions.* No physician or hospital shall be subject to civil liability based solely on the failure to obtain consent in rendering emergency health care to any person regardless of age where the patient is unable to give consent and no other person is available who is legally authorized to give consent—RCW 18.71.220.
2. *Venereal disease.* A minor aged 14 or older may consent to examination for and treatment of venereal disease—RCW Annotated (RCWA) 70.24.110.
3. *Drug abuse.* Any person 14 years or older may consent to counseling, care, treatment or rehabilitation by an approved drug or alcohol treatment center or a practitioner for drug or alcohol abuse. Parental consent is needed for residential treatment of a minor—RCWA 69.54.160.
4. *Contraception.* There are no specific laws, but the standard of practice has been for family planning centers to provide such services without parental consent, except in the insertion of intrauterine devices.

Confidentiality

Drug abuse. Records regarding drug or alcohol abuse treatment shall be confidential and information shall not be divulged without a patient's consent—RCWA 69.54.070. A minor's family shall be notified promptly of the minor's admission to a treatment facility—RCWA 70.968.120.

Payment

Venereal disease. Parents shall not be liable to pay for self-consenting minors—RCWA 70.240.110.

Drug abuse. Parents are not liable for payment for self-consenting minors unless parents have joined in the consent—RCWA 69.54.060.

Wyoming

In Wyoming teens may self-consent for health care[23] if they are

TABLE 1.—*Review of Consent Laws in Western United States*

State	Age of Majority, Years	May Consent for Medical Care: General Conditions	May Give Consent for Medical Care: Specific Conditions					
			Emergency	Contra-ception	Pregnancy Related	Venereal Disease Care	Substance Abuse	Other
Arizona	18	M or E	Yes	No	No	Yes	Age 12	Rape—age 12
California	18	M or E	Yes	Yes	Yes	Age 12	Yes	Rape—age 12, mental health treatment if mature and danger to self or others
Colorado	18	M or E	Yes	Yes	No	Yes	Yes	Rape
Idaho	18	...	Physician can consent	Yes*	No	Age 14	Age 16	...
Montana	18	M or E, parent, high school graduate	Yes	Yes	Yes	Yes	Yes	Urgent psychiatric care
Nevada	18	M or E	Yes	No	No	Yes	Yes	...
New Mexico	18	M or E	No	Yes*	Yes	Yes	Yes	Mental health treatment
Oregon	18	Age 15 or M	No	Yes	No	Yes	Yes	...
Utah	18	M	No	Yes	Yes	Yes	No	...
Washington	18	M	No	No	No	Age 14	Age 14	...
Wyoming	19	M	No	No	No	Yes	No	...

E=emancipated, M=married

*See text

- Older than age 19, the age of majority—Wyoming Statutes Annotated (WSA) 14-1-101.

Specific Circumstances

1. *Emergency conditions.* A minor may give consent when the parents cannot be located with reasonable diligence and the minor needs treatment that is sufficiently urgent to require immediate attention—WSA 14-1-101(b)(iii).
2. *Venereal disease.* Any person regardless of age may give consent for treatment of suspected venereal disease—WSA 34-4-131.

Confidentiality and Payment

There were no specific references to the areas of confidentiality and payment in the Wyoming statutes in regards to minors.

Summary

While consent and confidentiality laws for minors are clear in certain areas, many issues are ambiguous. As in many ethical questions, the provider is often dealing with two "rights"—the "right" to protect the privacy of a teen and the "right" for parents to know if their daughter is pregnant or having an abortion. When these two rights clash and parental involvement is refused, what should be done? The guidelines given in this article help clarify laws in individual states. Additional advice is available from state medical associations, local planned parenthood clinics or state attorney generals' offices. But at some point the physician is left without specific guidelines and must determine what is in the best interest of the patient.

This article should not be used as a definitive legal advice in individual cases. Discussions with local legal experts are advised for difficult cases. Consent laws are summarized in Table 1.

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Commentary

The Right Way to Go

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

There was great joy in the family when Deborah Kay came crying and kicking into my waiting hands late one night some 30 years ago this month. Two teenaged brothers and a 13-year-old sister knew they would now have a baby sister to play with.

For the baby's 40-year-old mother, the past nine months had been filled with mixed emotions. Nor had it been an easy time for the father. Well into their middle life, with three teenagers in the household, the couple had long ago put aside any thoughts of possible pregnancy. Contraception had been hit-or-miss. And they had missed. The pregnancy test had been positive.

At first there was anger and then panic. Husband accused wife; wife harangued husband. What would friends and relatives say? What will our kids think? Obviously, abortion was out of the question.

Slowly frustration gave way to resignation and then even to guarded happiness. Maybe a Higher Power meant them to have one more "bundle of joy." The teenaged boys, when Mom and Dad finally found the courage to tell them, shrieked, "Hey, that's cool!" The 13-year-old sister was jubilant, "I'll be the babysitter!"

Now, at long last, the day of deliverance was here. With the mother cared for, I turned to the new baby girl. She was chubby, a little puffy, with the hint of a different look about her. But newborn babies, with their molded heads and their squeezed faces, are anything but pretty. Anyhow, she was alive and well, with an Apgar of 8 to 9. I would check her over more carefully on morning rounds. It was 2 AM and maybe I could catch a few winks.

"There's something peculiar about this little one you delivered this morning, Doctor," was Nurse Joan's comment as she brought Deborah Kay to me to examine. Sure enough, the baby's face was still puffy and there was something about her eyes: slanted and almond-shaped. The nose was flat and there was a tiny split in the tip of her tongue. Her fingers so stubby, legs so lax—surely we had to give serious consideration to a diagnosis of Down's syndrome.

Joan made the natural agonized response, "Oh, no, what will we tell the mother?" "Well," I said, "first of all, we won't make any statements until we are absolutely certain of the diagnosis. And, second, let's make sure we use the proper name: 'Down's syndrome,' not 'mongolism.'"

As we expected, all the tests confirmed the diagnosis of trisomy 21, that birth defect caused by one little extra 21st chromosome in mother's egg. Now I would have to face Mom and Dad with the bad news.

It was not easy. After I had finished telling them that Deborah Kay would have these defects, that she would be mentally retarded and that she would live a life of utter dependency, there was only tearful silence. Then . . . "You're very, very sure, are you, Doctor?" asked Mother as she cradled her infant to the warmth of her breast. I explained all the different tests we had used to arrive at the final diagnosis. Hurrying on, I suggested that in instances such as this, parents often decide to place these little ones in institutions, and that this would be a choice they would be entitled to make.

Mom and Dad looked at me in bewilderment. "Doctor, do you know what you are saying? This is *our* baby. No way will we give her up!"

So it was that Deborah Kay went home into the loving arms of a family welded together by the need to cherish and care for and protect this little person, who would live her life in perpetual childhood, never attaining true womanhood.

Bringing up Debbie was not always easy; her mental and physical inadequacies called for special efforts and lots of patience on the part of every member of the family. As an infant she clung to breast-feeding until she was a year and a half. Mom drew on her reserve strength to give the little one the security of her bosom. Teaching Deborah to eat with a fork and spoon went slowly; fingers seemed to work so well. On the one hand, personal matters such as toilet training and perineal hygiene were treated with exasperating indifference by this young lady, while, on the other hand, the first menstruation was a terrifying experience: "Mommy, am I going to die?"

Because Debbie was slow and awkward, other children would laugh at her, taunt her, run away from her. As a result brothers and sisters and Mom and Dad would set aside time to be her surrogate playmates. In return, over the years she showered them all with her smiles and hugs and with those funny, babbled sentences. More than that, she gave them a most precious reward: total devotion, limitless love. And with that the family was given a sense of fulfillment at having accepted the responsibility for the complete care of another human being.

Just last week Debbie and her 43-year-old sister came in for their routine physical examinations. As always, the word was, "Debbie gets to go first." And once again Debbie twinkled her charming, tongue-between-the-lips smile at me and trustingly lay back for her complete examination.

At last year's checkup I had noted an enlarged uterus, and because her extremely heavy periods had resulted in a secondary anemia, we had given some consideration to doing a

(Fox ERW: The right way to go. West J Med 1987 Aug; 147:225-226)

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hysterectomy. Today I found the uterus had diminished in size, and sister reported that the periods had stopped completely. Nature at work.

The rest of Debbie's examination showed only the evidence of advancing years—the thinning of her skin, the atrophy of her breasts, the further loss of height, the "widow's hump."

How ironic it is, I thought, as I went through a similar examination of her older sister, that here today is the teenager who at age 13 had happily promised to be the new baby's "babysitter," and who through the past 30 years had been just that, even after she had married and reared her own family.

Yet here was stunted Debbie, whose body I had been privileged to look after as she went through infancy, puberty, the middle years and now menopause, in a span of only 30 years. Here was a person whose entire being had been imprisoned in a fruitless childhood. But during those years what blessings of togetherness she had brought to this fine family as they nurtured her and protected her. How fortunate it was that 30 years ago Mom and Dad had made that wise decision to take her home.

Having finished the afternoon appointments, it was time to lean back, stretch my legs and let my thoughts roam, reviewing the patients and the problems I had dealt with that day. Especially vivid was the vignette in which Debbie had played the leading part. In my mind I tried to transpose the events of 1957 into circa 1987. Had the 40-year-old pregnant woman come into my office today, instead of 30 years ago, how would my treatment have differed?

Obviously, in this day of enlightenment, that intelligent lady would be well aware of the possibility that the embryo she was carrying in her uterus might be defective. She would know also that I, as her physician, would offer her the option of having an amniocentesis done and that she might then be offered an abortion.

For me the specter of professional liability would have hovered over my head. What if the test failed or proved inaccurate, or what if the amniocentesis inadvertently caused the disruption of a normal pregnancy? Surely, if the pregnancy were to be allowed to continue, the weight of uncertainty would weigh upon me right up until the time of delivery.

Would these two people—husband and wife—who were beginning to feel great joy at the prospect of having a treasured "late-in-life" baby, now have to suffer the anguish of making a decision, one that might plague them all the days of their lives, whichever course they chose?

Right now it was easy for me to say that the way we went back in 1957 was the right way, having seen Debbie's life unfold in the tender embrace of a devoted family. Moreover, 30 years ago the choices were not that hard to make; Debbie's parents knew there was just one way to go. Today the way is strewn with sharp stumbling blocks. Debbie's embryo would be the concern, not only of the parents and the doctor, but possibly of the courts, the legislature and the bioethics committee.

Today, why must it be so hard to know—the right way to go?

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(Continued from Page 155)

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September 20—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-22—**7th Annual Bristol-Myers Symposium on Nutrition Research: Nutrition and the Origins of Disease.** UCD at Fairmont Hotel, San Francisco. Mon-Tues. 15 hrs. $100. Contact: UCD.

September 30—**Drug Therapy for Ventricular Arrhythmias.** Regional Arrhythmia Center at Cedars-Sinai Medical Center, Los Angeles. Wed. 5 hrs. Contact: Lore Kahane, Cedars-Sinai Medical Center, 8700 Alden Dr, Los Angeles 90048. (213) 855-5547.

October 9-10—**Twelfth Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute, Dominican Hospital at Chaminate Conference Center, Santa Cruz. Fri-Sat. $300. Contact: Karen Rickenbach, Dominican Neurologic Institute, Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7706.

October 14—**17th Annual Respiratory Medicine.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

October 16-18—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $365. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-22—**Annual Family Practice Update.** Mon-Thurs. LLU at LLU. Contact: LLU.

October 19-30—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI at Long Beach. Mon-Fri. Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

October 22-24—**West Coast Counties Postgraduate Institute.** California Medical Association at Sheraton Hotel, Monterey. Thurs-Sat. 12 hrs. Contact: Janice Rigney, CMA, PO Box 7690, San Francisco 94120-7690. (415) 863-5522, ext. 416.

October 26-November 1—**Traumatic Brain Injury.** UCD at Red Lion Motor Inn, Sacramento. Mon-Sun. Contact: UCD.

November 12-14—**2nd Annual: Progress in Impotence—Workshops/Seminars.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. 13 hrs. $295. Contact: Edith Bookstein/UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 18—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service, (117) VAMC, 16111 Plummer St, Sepulveda 91343. (818) 891-2473.

November 22—**Controversy in Modern Medicine—1987.** Granada Hills Community Hospital and UCLA at Sheraton Universal Hotel, N Hollywood. Sun. 7 hrs. $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 228)

December 7-18—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

IDAHO

August 13-15—**Sun Valley Emergency Medical Conference.** Convention Center, Sun Valley. Thurs-Sat. Contact: Idaho EMS System, 450 W State St, Boise 83720. (208) 334-5994.

MONTANA

October 1-3—**Montana Medical Association—Annual Meeting.** Copper King Inn, Butte. Thurs-Sat. Contact: MMA, 2012 11th Ave, Ste 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 11-13—**Essentials of Health Care for the Elderly.** UNM Conference Center, Albuquerque. Fri-Sun. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

September 19—**Practical Management of Diabetic Foot Infections.** Veterans Administration Medical Center, Albuquerque. Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

September 24-26—**Concepts and Controversies in Perinatal Care.** Holiday Inn Journal Center, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME. (505) 277-3942.

September 24-26—**Wilson Lectureship—Cardiology Symposium.** Albuquerque. Thurs-Sat. Contact: Presbyterian Heart Institute Cardiology Symposium, PO Box 26666, Albuquerque 87125. (505) 841-1065.

October 1-3—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

October 10-11—**Pediatric Chronic Diseases.** Santa Fe. Sat-Sun. Contact: Marilyn Stack, Executive Secretary, New Mexico Pediatric Society, (505) 265-7431.

October 23—**Update in Cardiology.** Albuquerque. Fri. Contact: Charles Karaian, MD, 1101 Medical Arts Ave NE, Albuquerque 87102. (505) 842-8321.

October 23-25—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Fri-Sun. Contact: The Presbyterian Heart Institute, Barry W. Ramo, MD, (505) 242-2796.

November 13-14—**New Mexico Medical Society Interim Meeting—Risk Management.** Sally Port Inn, Roswell. Fri-Sat. Contact: NMMS, (505) 266-7868.

December 3-5—**American College of Physicians, New Mexico Chapter—Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

December 11-12—**Trauma Update '87.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

(Continued on Page 230)

Saint Joseph Cancer Center
Burbank, California
presents

Breast Cancer 1987: Update on Clinical Practice

Screening • Diagnosis • Treatment Modalities • Community Practices

Friday and Saturday, November 6–7
Century Plaza Hotel
Los Angeles, California

These and other nationally known speakers will discuss breast cancer screening and diagnosis, therapy for minimal and advanced stages, and patterns of community care:

Gianni Bonadonna, MD
Director, Institute Nationale
Per Lo Studio E La Cura Dei Tumori
Milan, Italy

George Canellos, MD
Chief, Division of Medical Oncology
Dana Farber Cancer Center, Boston

Vincent DeVita, MD
Director, National Cancer Institute
Bethesda, MD

Bernard Fisher, MD
Project Chairman, NSABP Trials
Pittsburgh, PA

Samuel Hellman, MD
Physician-in-Chief
Sloan Kettering Cancer Center, NY

Thomas Krizek, MD
Prof. and Chrmn., Dept. of Surgery
Section of Plastic & Reconstructive Surgery
University of Chicago, IL

Robert McDivitt, MD
Professor of Pathology
Washington Univ. Medical Center
St. Louis, MO

William Silen, MD
Johnson & Johnson Professor of Surgery
Harvard Medical School, Boston, MA

Philip Strax, MD
Medical Consultant
Strax Breast Cancer Detection Institute
Fort Lauderdale, FL

$300 for two days / $185 for one day
Approved for up to 12 CMA Category 1 CME credit hours and the AMA Physicians' Recognition Award

Held in cooperation with the American Cancer Society San Fernando Valley Unit

Call Helen F. McGrane, PhD, Saint Joseph Medical Center
818 / 843-5111, ext. 7241, 7481

Saint Joseph Cancer Center is a part of Saint Joseph Medical Center
Buena Vista & Alameda Sts., Burbank, CA 91505

Sisters of Providence—Serving in the West Since 1856

(Continued from Page 229)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

August 24-28—**Occupational Epidemiology** (Sponsor: UUMC). Mon-Fri. College of Nursing, Univ of Utah, Salt Lake City. 32.5 hrs. Contact: Connie Crandall, (801) 581-5710.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: Latter-Day Saints Hospital, 325 8th Ave, Salt Lake City 84143. (801) 350-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 N Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

August 31-September 4—**Environmental Epidemiology and Risk Assessment** (Sponsor: UUMC). Mon-Fri. College of Nursing, Univ of Utah, Salt Lake City. 32.5 hrs. Contact: Connie Crandall, (801) 581-5710.

September 9-11—**Utah State Medical Association Annual Meeting.** Marriott Hotel, Salt Lake City. Wed-Fri. Contact: USMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-5290.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

August 20-21—**Plastic Surgery: Lectures and Workshops on the Techniques of Small Excisions and Wound Management.** Seattle. Thurs-Fri. Contact: U/W.

August 20-22—**Imaging on Lake Coeur d'Alene.** Coeur d'Alene. Thurs-Sat. Contact: Sacred Heart Medical Center, (509) 455-3352.

September 11—**Patient Controlled Analgesia.** Seattle. Fri. Contact: U/W.

September 11—**Depression: Update '88.** Seattle. Fri. Contact: U/W.

September 14-18—**Primary Care: Skills and Knowledge.** Presented by the Department of Family Medicine. Seattle. Mon-Fri. Contact: U/W.

September 21-22—**Total Hip Replacement.** The Inn at Semiahmoo, Blaine. Mon-Tues. Contact: U/W.

October 1-2—**American College of Emergency Physicians—17th Annual Fall Scientific Assembly.** Seattle. Thurs-Fri. Bellevue Red Lion Inn. Contact: Washington Chap, ACEP, (206) 441-9762.

October 14—**Psychological Aspects of Occupational Health.** Seattle. Wed. Contact: UW, (206) 543-1069.

October 15-17—**Annual Review of Neurosurgery.** Seattle. Thurs-Sat. Contact: U/W.

October 16—**Psychosis: What's New, What's True.** Seattle. Fri. Contact: U/W.

October 16—**21st Annual Cancer Conference: Breast Cancer—Issues Faced by the Primary Care Physician & Patient.** Seattle. Fri. Contact: VMMC.

October 29-31—**Orthopedic Review.** Seattle. Thus-Sat. Contact: VMMC.

November 27-December 10—**Emergency and Critical Care Downunder.** Sites in New Zealand and Australia. Fri-Thurs. Contact: Washington Chapter, American College of Emergency Physicians, Georgine Elich, Kailani World Travel, 1 (800) 542-5264 or (206) 671-1800. ◆

A Clinical Opportunity for Smoking Intervention

You can play a special role in reaching smokers. Encouraging parents not to smoke can improve the health of the entire family.

Take a few minutes to explain that children of parents who smoke are often more prone to respiratory infections. Tell them that young children of parents who smoke are more likely to become smokers themselves.

The minutes you spend can make a difference now, and in the years ahead.

For a free copy of *Clinical Opportunities for Smoking Intervention: A Guide for the Busy Physician*, complete the form below.

Mail to:
The National Heart, Lung, and Blood Institute
Smoking Education Program
National Institutes of Health
Building 31, Room 4A 18
Department P-09
Bethesda, MD 20892

Name

Specialty

Address

City

State, Zip

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NORTHERN CALIFORNIA. FP/IM physicians needed to staff ambulatory care clinics in the Central Valley region of California. Paid malpractice and excellent benefit package. Incentive plus guarantee. If interested, please contact SEMG, PO Box 214584, Sacramento, CA 95821.

FAMILY PRACTITIONER. Full-time BE/BC FP for growing multispecialty group in sunny California. Some Spanish helpful. First year compensation, benefits, and malpractice. Partnership potential second year. Send CV to Number 29, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEAR STANFORD. Six Internists, all sub-specialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

FAMILY PRACTICE. Excellent professional opportunity in beautiful north Idaho. Nominal lease at hospital owned clinic includes fully-equipped office, treatment suites and general receptionist. X-ray, lab and pharmacy on site. Located in 4-season playground rich with recreational opportunities. For information call Nancy at (208) 784-1221, ext 304, or send résumé to Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

ORTHOPEDIC SURGEON. Full-time Orthopedic Surgeon to join growing multispecialty group in sunny California. Salary, incentive, malpractice and benefits. Great potential for right physician. Individual ownership. Send CV to Number 30, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE. Full-time BE/BC active Internist for multispecialty group in sunny California. Office/hospital and consult practice. Spanish a plus. Salary, benefits, and malpractice. Potential for partnership second year. Send CV to Number 31, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST position available with 35 member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to Colin J. Wells, MD, San Luis Medical Clinic, Ltd, 1235 Osos St, San Luis Obispo, CA 93401-3619. NO PHONE CALLS PLEASE.

PHYSICIANS WANTED

CALIFORNIA FORENSIC MEDICAL GROUP, INC, a corporation providing medical services in California county jails, has opportunities for physicians with a specialty in either Family Practice, General Practice or Internal Medicine. Send résumé to CFMG, Inc, PO Box 1831, Salinas, CA 93902; or contact Elaine Hustedt (408) 422-0214.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

MINNEAPOLIS. Seeks BC/BE associates in Adult Psychiatry, Cardiology, Family Practice, Internal Medicine, Obstetrics and Gynecology and Urology. Practice quality medicine in a prepaid multispecialty setting located in one of America's leading metropolitan areas. Comprehensive benefits, excellent facilities, flexible compensation programs. For further information about joining the Group Health medical staff, call Jerry Hess at (612) 623-8444 or write to Group Health, Inc, Attn: Jerry Hess, 2829 University Ave, SE, Minneapolis, MN 55414.

PHYSICIAN RECRUITMENT. Position available in San Francisco Area Medical Network, seeking physician with an interest in a stable, long-term practice opportunity in ambulatory care. Enjoy the advantages of private practice without the cost and complications. Candidate must be BC/BE in either Family Practice or Internal Medicine. Interested-send CV to Dr Susann Steinberg, 5748 Geary Blvd, San Francisco, CA 94121; (415) 668-4005.

PHYSICIANS WANTED

HOUSE PHYSICIAN

Seeking qualified M.D. to provide immediate full- or part-time day (8 am – 5 pm) coverage of ICU and other medical inpatients. Starting date: September 1, 1987. Minimum training required: internship and 2 years of internal medicine residency.

Contact Alan Rosenstein, M.D., Director of Patient Care

Marshal Hale Memorial Hospital

3773 Sacramento Street
San Francisco, CA 94118
(415) 386-7000

GENERAL SURGEON. Excellent opportunity for BC/BE in General Surgery. Close to San Francisco in beautiful wine country. Reply to Number 38, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SALT LAKE AREA. General Practitioner needed for new, fully-equipped facility. Excellent salary—benefit package, plus percentage. Enjoy outdoor recreation, skiing, hunting, fishing, as well as cosmopolitan living. Reply to Number 34, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE IN IDAHO? Join four physicians and nine nurse practitioners in an exciting clinic system. One position available in September 1987. Attractive salary and benefit package. Contact Erwin B. Teuber, PhD, Administrator, or Robert LeBow, MD, Medical Director, Terry Reilly Health Services, 211 16th Ave North, Nampa, ID 83651; (208) 467-4431.

FAMILY PHYSICIAN. BC/BE, residency-trained, to join group in Santa Fe, New Mexico. Practice includes obstetrics and after-hours care. $40,000, incentive. Reply to Number 46, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPAEDICS. Excellent private practice opportunities currently available in New Mexico and Colorado communities. Income guarantee/financial assistance available; relocation allowance provided. Wide range of recreational opportunities. For further information, please contact Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

ARIZONA EMERGENCY MEDICINE. An emergency department Medical Directorship and staff positions are immediately available at two client hospitals located in Kingman and Lake Havasu City. Moderate volume emergency departments. Excellent nursing and medical staff support. We offer a guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. Directors also receive paid health benefits which include dependents. For additional information contact George Tracy, Spectrum Emergency Care, 6275 Lehman Dr, Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

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PHYSICIANS WANTED

FAMILY PRACTICE/INTERNAL MEDICINE/ENDOCRINOLOGY/CARDIOLOGY/OCCUPATIONAL MEDICINE physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing southwest community (population 500,000 plus). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics/Internal Medicine/Subspecialties/24-hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with CV to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645.

CALIFORNIA, SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for high-volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of 20 full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation; one week CME; paid malpractice, health and life insurance; corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

NEONATOLOGIST. Member of 28-physician, multispecialty group in North Dakota. 250-bed hospital with fully-equipped Level III unit. Excellent salary plus bonus. Contact Jean Malkasian, 250 Regency Ct, Waukesha, WI 53186, or (414) 785-6500, collect.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full- or part-time for FP/IM/EM trained/experienced physician. Located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900-100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or (206) 582-2542.

CALIFORNIA, MERCED. Emergency Department medical directorship and full-time staff opportunities are available at our client hospital in Merced. Full-service community hospital with moderate volume ED. Guaranteed rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues, relocation allowance. Must be willing to live in community. For additional details contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr, Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

ORTHOPEDIC SURGEON. Opportunities throughout the midwest and Colorado. These positions offer both general orthopedic practices, along with subspecialized training. Partnership and group settings. Contact Jean Malkasian, 250 Regency Ct, Waukesha, WI 53186; (414) 785-6500, collect.

ANESTHESIOLOGIST sought for the Española Hospital in Española, New Mexico. Financial assistance with income guarantee. For further information, please submit CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

PEDIATRICIAN/COLORADO. A Pediatrician is needed in the fast-growing northern Denver suburb of Thornton. Offices located next to our 172-bed Humana Hospital—Mountain View. Attractive financial package. Send your CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free (800) 626-1590.

(Continued on Page 244)

THE ARMY NEEDS PHYSICIANS PART-TIME.

If you are a practicing physician who wants a break from your daily practice . . . while still practicing high-quality medicine and serving your country . . . consider an officer commission in the ARMY RESERVE MEDICAL CORPS.

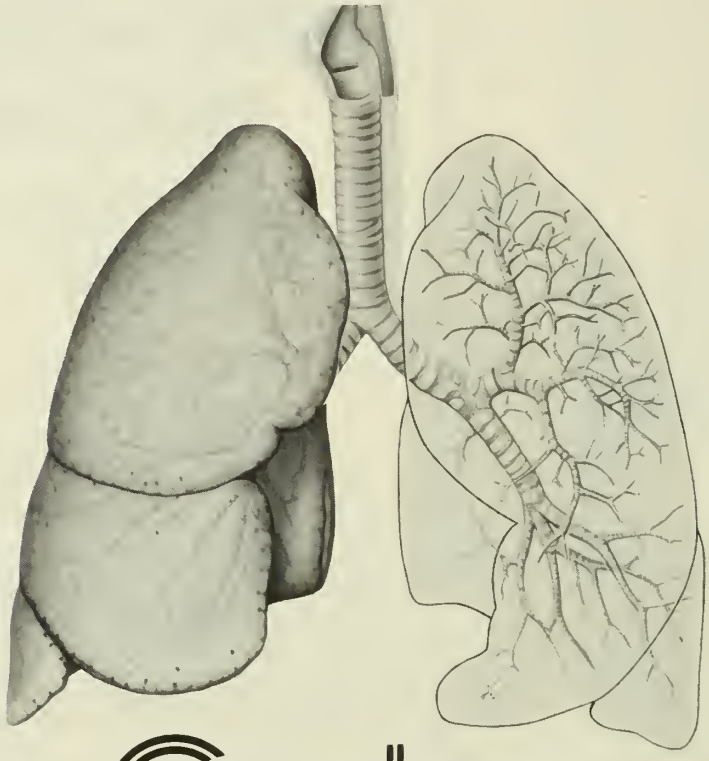
AMONG THE BENEFITS:

- Subsidized professional development which could include two conferences/short courses of your choice.
- Up to $50,000 Group Life Insurance package, nominally priced for qualifying MD's, generous retirement annuity to qualifying physicians at age 60.
- Monthly stipend for local professional services.
- Post Exchange, Commissary (during Annual Training) and space-available travel on military aircraft.
- Flexible training programs that won't interfere with your practice.

To see if you qualify contact:

Major Patricia S. Schackleton, MSC	415-751-1616
Major Michael F. Lyons, MSC	213-474-0138
Captain Gregory F. Linden, MSC	619-453-9937

Consider the causative organisms...



Ceclor®
cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae, Streptococcus pneumoniae
(ampicillin-susceptible and ampicillin-resistant)

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins.

Warnings:
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

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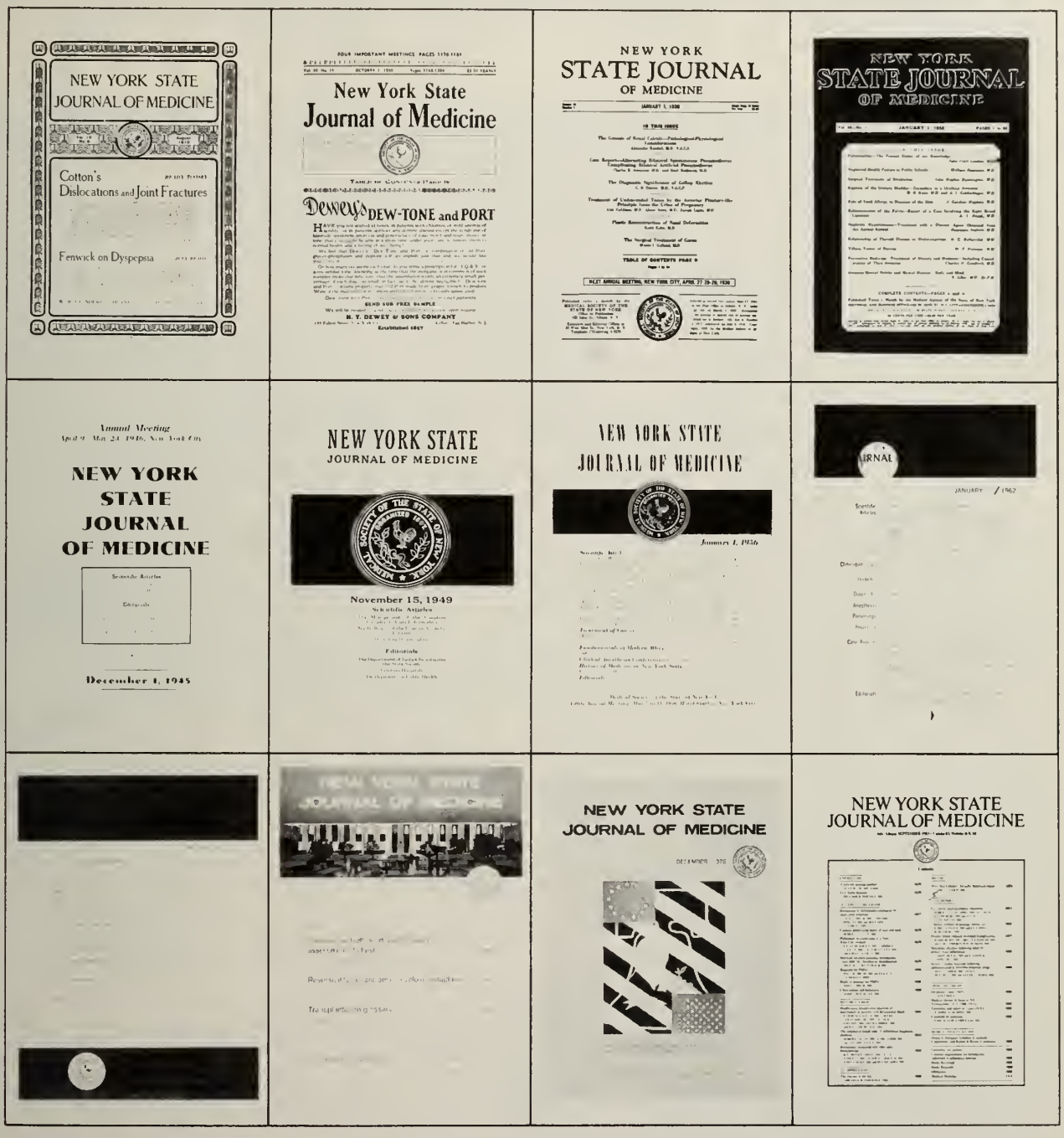

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For a complete discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary on adjacent page.

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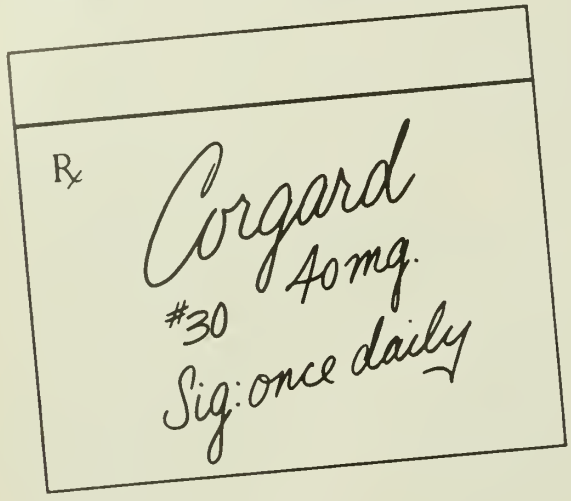

CORGARD® TABLETS
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DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

(J4-156)

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)" and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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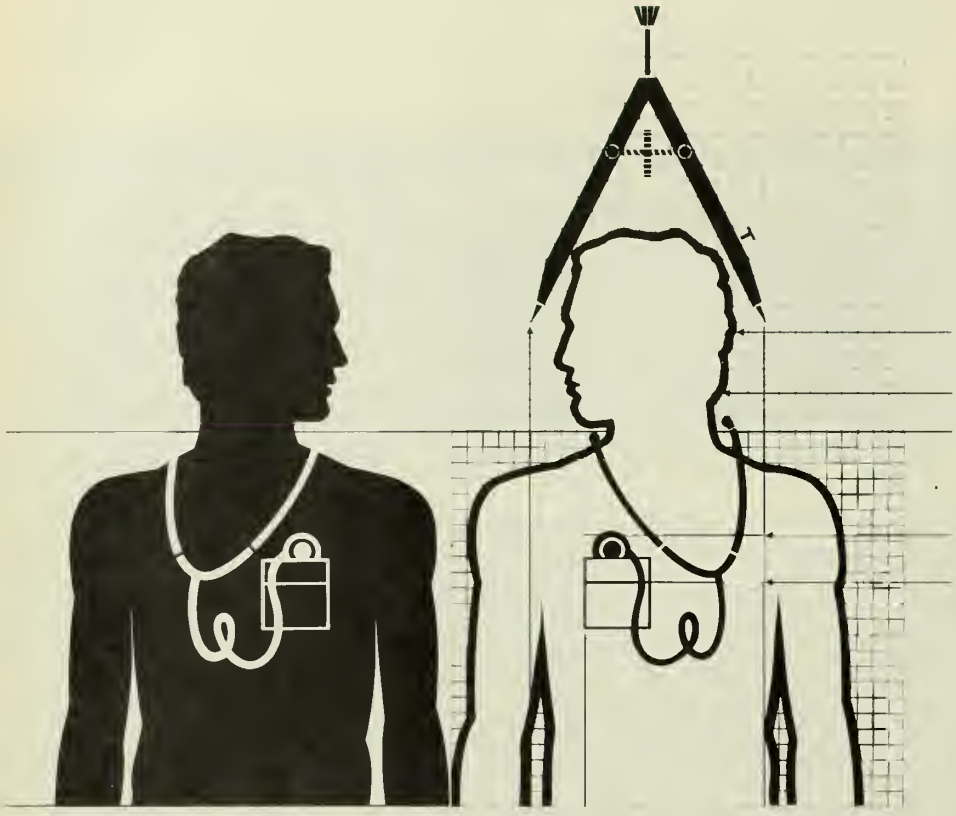

UTAH MEDICAL ASSOCIATION ANNUAL MEETING

September 9-10-11, 1987
Marriott Hotel,
Salt Lake City, UT

Schedule

Wednesday - September 9

8:30 a.m. - 4:00 p.m.	House of Delegates
12:00 noon	Luncheon William S. Hotchkiss, M.D. President, American Medical Association
6:30 p.m.	President's Reception and Banquet

Thursday - September 10

8:30 a.m. - 12:00 noon	Forum on Medical Issues **"Measuring the Doctor"**
2:00-4:45 p.m.	**Doctors in the Courtroom: Dealing With the Emotional Costs**
5:00-6:30 p.m.	Social hosted by Young Physicians and Women Physicians Sections

Thursday Evening

6:30 p.m.	Specialty Society Dinners Utah Chapter American College of Physicians Leadership Dinner
6:30 p.m.	Western Orthopedic Association Quarterly Dinner
6:30 p.m.	Obstetrical Required Education Meeting for UMIA Insured Physicians
6:30 p.m.	Utah Urological Society Dinner

Friday - September 11

8:00 a.m. - 4:30 p.m.	**Scientific Programs** American College of Physicians & Utah Society of Internal Medicine Utah OB-GYN Society Utah Psychiatric Association
6:30 p.m.	Utah OB-GYN Society Dinner
6:30 p.m.	Utah Society of Anesthesiologists Dinner

Saturday - September 12

8:00 a.m. - 12:00 noon	Utah Society of Anesthesiologists Meeting

Program Descriptions

Forum on Medical Issues "Measuring the Doctor"

Thursday - September 10, 1987

8:30 a.m. - 12:00 noon

A variety of quality assurance systems are emerging which will measure outcomes, assess clinical procedures, and test physicians in their practice of medicine. The FORUM ON MEDICAL ISSUES will present prominent speakers who will discuss these emerging systems and how they will affect physicians.

Moderator: Alan R. Nelson, M.D., Chairman of the Board, American Medical Association

Doctor Nelson was elected to the AMA Board of Trustees in 1980 and is Chairman of the Board. He also serves as an AMA Commissioner to the Joint Commission on Accreditation of Hospitals and is Chairman of the AMA Commissioners. Dr. Nelson has published numerous papers and several book chapters on medical peer review and quality assurance.

U.S. Government: Kayleen Drissell
Regional Inspector General
Department of Health & Human Services

As Regional Inspector General for investigations over the Denver Region, Ms. Drissell oversees the Department of Health and Human Services (DHHS) investigative functions in a ten-state region, including the state of Utah. She has been a Federal criminal investigator, first with the FBI and currently with the Office of the Inspector General, for 14 years.

Joint Commission on Accreditation of Hospitals: James S. Roberts, M.D., Senior Vice President, Research and Planning

American Medical Association: John Dawson, M.D., Board of Trustees
Quality Assurance

Doctor Dawson, a general surgeon from Seattle, Washington, was elected to the AMA Board of Trustees in 1983 and reelected in 1984. He serves as an AMA Commissioner to the Joint Commission on the Accreditation of Hospitals. Dr. Dawson was a member of the AMA Council on Medical Service and is a Past President of King County Medical Society and Past President of the National Christian Medical Society.

Doctor Roberts joined the staff of the Joint Commission on Accreditation of Hospitals in 1979. He is now Senior Vice President for Research and Planning where his efforts have been focused on quality review and evaluation of health professions. Dr. Roberts has published numerous papers concerning evaluation and review of physicians.

Business & Consumers: James Mortimer, President
Midwest Business Group
Quality Assurance Guidelines for
Business Purchasers

Mr. Mortimer organized the Midwest Business Group on Health in 1980 to create a vehicle to help employers manage benefit plan costs. The Group now has 160 member employers and spans a nine-state region. Mr. Mortimer currently is on the U.S. Chamber of Commerce Management, Labor and Employee Benefit Committee.

Doctors in the Courtroom: Dealing with the Emotional Costs

Thursday - September 10, 1987 2:00-4:45 p.m.

Panel presenters discuss the emotional impact of professional liability litigation and how physicians can deal with it.

SARA C. CHARLES, M.D.
Associate professor of clinical psychiatry at the University of Illinois College of Medicine in Chicago, Dr. Charles is coauthor of **Defendant: A Psychiatrist on Trial for Medical Malpractice**, published by Random House in 1986.

DON ORSILLO, Ph.D.
A specialist in the psychology of jury attitude, Dr. Orsillo has served as a consultant to large corporations and defense counsel in medical liability and other tort litigation.

ELLIOTT J. WILLIAMS, J.D.
A prominent Salt Lake defense lawyer, Mr. Williams is general counsel for the Utah Medical Insurance Association.

Specialty Society Scientific Meetings

Utah Chapter ACP Scientific Meeting In Association with the Utah Society of Internal Medicine

Friday, September 11, 1987 8:00 a.m. - 5:00 p.m.

- Management Strategies for Acute Myocardial Infarction
- Office Dermatology for the Internist
- Nephrology — 1987
- AIDS: New Developments
- Immunization for Adults
- Cardiac Transplantation in Utah

Utah Psychiatric Association

Sessions are provided in cooperation with the American Psychiatric Association for primary care physicians.

Friday, September 11, 1987 8:30 a.m. - 3:00 p.m.

dentification and Treatment of Depression

Diagnosis & Treatment of Substance Abuse in Adolescents

Utah Obstetrical & Gynecological Society

Friday, September 11, 1987 7:30 a.m. - 5:15 p.m.

Improving Medical Skills Beyond Excellence:
Facing the Difficult Patient and
the Difficult Medical Dilemma

Conference provides an innovative, hands-on learning experience for practicing physicians in obstetrics and pediatrics. Practical methods for dealing with the difficult patient and team management of a poor outcome resulting from a C-section with full newborn resuscitation will be included.

For additional information and registration, contact the Utah Medical Association (801) 355-7477.

(Continued from Page 233)

PHYSICIANS WANTED

NORTHERN SAN DIEGO, CALIFORNIA. General Internist with interest in Geriatrics needed to join same at small satellite of large medical group. Excellent opportunity. Send CV to Scripps Clinic Welk Village, 8885 Lawrence Welk Dr, Escondido, CA 92026; (619) 749-8787.

UNIQUE COLORADO/ARIZONA OPPORTUNITY. Daytime hours; better than average compensation; full- or part-time. Send CV or correspondence to John D. Ferris, MD, PC, 3400 Industrial Lane, Ste 5-B, Broomfield, CO 80020, or call (303) 465-2400.

ARIZONA, PHOENIX, PRIVATE PRACTICE. Six figure guarantee, no financial risk, option to buy, replies held in confidence. Contact Fran Peters (313) 552-0320, call collect. (Not a search firm.)

PERSONABLE PHYSICIAN needed for an established ambulatory medical care facility in the beautiful northwest. Opportunity for profit sharing and partnership. Send CV to Steve Thomas, MD, Spokane First Care Med-Centers, Inc, P.S., North 312 Mullan Rd, Spokane, WA 99206; or phone 1 (509) 928-1613.

ASSISTANT ASSOCIATE PROGRAM DIRECTOR FOR FAMILY PRACTICE PROGRAM. Must have AAFP Boards. Would like private practice experience, but will evaluate applicant's overall strengths and will waive practice requirement in selected candidates. Strong program. University (University of California, Davis) affiliated. Excellent opportunities in research, curriculum development, and teaching of clinical skills. Call or send CV to Bruce Nichols, MD, Director of Family Practice, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6834. AA/EOE.

IDAHO NEEDS FULL-TIME EMERGENCY PHYSICIAN. 20 miles from Boise, near mountains and unlimited recreation. Excellent opportunity to affiliate with 162-bed hospital. ACLS-yes. Contact M. Kutsurelis, Vice President Administrative Services, Mercy Medical Center, 1512 12th Ave Road, Nampa, ID 83651; (208) 467-1171.

THE COMMUNITY OF ARTESIA, NEW MEXICO is seeking a Board certified or eligible General Surgeon to establish a private practice. Fully-equipped office with established referral patterns available for purchase. Community-based financial assistance may be available to the right individual. Artesia is a community of 14,000 located in southeast New Mexico. A great place to raise a family—peaceful community with year 'round recreation and excellent weather. Fully-equipped, 38-bed new hospital. Please submit CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

GENERAL SURGEON BC/BE. Excellent opportunity to associate in a busy surgical practice in Sonoma, California, one hour drive north of San Francisco. Contact J. Basil Haddad, MD, 181 Andrieux St, Sonoma, CA 95476; (707) 996-6119.

FAMILY PRACTICE PHYSICIAN—SANTA FE, NEW MEXICO. BC/BE, six months OB training. Share call with two MDs. Much obstetrics. Send CV to Arturo Gonzales, La Familia Medical Center, PO Box 5395, Santa Fe, New Mexico 87501; (505) 982-4427.

SEEKING A PHYSICIAN TO ASSOCIATE with a Family Practice group. Ultramodern facility with outpatient surgical suite. Located in Corona, California, between Orange County and San Diego. Growing area; good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes, (714) 734-3042.

BC/BE INTERNIST OR FAMILY PHYSICIAN needed for busy multispecialty group in Durgano, Colorado. Practice next to hospital, beautiful surroundings; benefits provided. Contact Bonnie DuPuis, PO Box 2637, Durango, CO 81302, or call (303) 247-2611.

PHYSICIANS WANTED

WASHINGTON STATE

The Wenatchee Valley Clinic, a multispecialty group of 105 physicians, has several practice opportunities throughout its seven practice locations. Currently we are seeking:

MAIN FACILITY—WENATCHEE

- **Pediatrics**
- **Allergy**
- **Nephrology**
- **Psychiatry**
- **General Internal Medicine**

SATELLITE FACILITIES—OMAK/MOSES LAKE

- **Orthopedics**
- **General Surgery**
- **General Internal Medicine**
- **OB/GYN**
- **Radiology**

All positions offer an excellent compensation and benefit package. North central Washington provides a high quality of life for those interested in an abundance of recreational opportunities in a family-oriented rural setting. If interested, send your CV to Dr Gerald Gibbons, Medical Director, Wenatchee Valley Clinic, 820 N. Chelan Ave, Wenatchee, WA 98801, or call (509) 663-8711, ext 205.

EDMONDS, WASHINGTON. Scenic waterfront community 20 minutes north of Seattle. Physician owned clinic combined OB/GYN and Family Practice seeks additional OB/GYN for full- or part-time. We presently have 4 Family Practitioners and 2 OB/GYNs. Send CV to Philip DuBois, MD, 7935 216th St SW, Ste E, Edmonds, WA 98020; (206) 775-0681.

SAN FRANCISCO—ONE HOUR. Multispecialty group in a growing community is now accepting applications for positions available in Family Practice and Internal Medicine. First year includes guaranteed salary plus incentive. Excellent benefits including malpractice, life, health and disability insurance. Send CV to Number 51, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OUTSTANDING POSITIONS AVAILABLE for BE/BC FPs in choice locations, throughout west/midwest. Group, solo, and partnership situations—generous financial and benefits package. Reply in confidence: Physicians International, 4-FP Vermont St, Buffalo, NY 14213; (716) 884-3700.

DIRECTOR OF THE RESIDENCY TRAINING PROGRAM. Full-time faculty position available in the Department of Family Practice, University of California, Davis. Level of appointment commensurate with academic experience and credentials. Must be Board certified by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research and academic publication activities. The position will remain open until filled. Applications will not be accepted after December 31, 1987. Send CV to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

NONINVASIVE CARDIOLOGIST—BC/BE to join busy Invasive Cardiologist in San Jose, California. Early partnership. Expertise required in all noninvasive activities including: Nuclear Cardiology, 2D-Doppler and echo. Also, Swan-Ganz and pacemaker insertion. Please send CV to Number 50, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEUROLOGIST/ANCHORAGE, ALASKA. Outstanding solo private practice opportunity available with option to share offices with one of three busy solo Neurologists, who will provide cross coverage. Offices are located adjacent to our 238-bed hospital. Anchorage, population 200,000 plus, is the hub of the state of Alaska and a sportsman's paradise. For further information call toll-free (800) 626-1590, or send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438.

PHYSICIANS WANTED

FAMILY PRACTICE PHYSICIAN. Full-time, in walk-in medical clinic, Visalia, Tulare County, California. Salary, malpractice insurance, etc. For additional information, contact Brenda Baker, Director of Business Services, (209) 627-5555.

BC/BE PEDIATRICIAN to join well-established, growing, six-pediatrician practice. Outstanding location in beautiful Washington state, Puget Sound area. Reply with CV to Patsy Caputo, Clinic Manager, 2625 Wheaton Way, Bremerton, WA 98310; (206) 479-1651.

UROLOGIST/PHOENIX, ARIZONA. A busy, 39-year-old Urologist is seeking an associate to join his thriving private practice. The offices are located near our new hospital in suburban Paradise Valley. For more specific information, call toll-free (800) 626-1590, or send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438.

OCCUPATIONAL MEDICAL PHYSICIAN sought to join expanding group treating a wide variety of industrial medical illnesses and injuries specializing in acute care. Excellent local contact with large employers. Incentives, profit sharing and other benefits. Competitive salary based on experience and commitment to our practice. Central San Joaquin Valley location with superb recreational opportunities and fine environment for family. Contact Occupational Health Associates, 125 E. Barstow, Ste 135, Fresno, CA 93710.

PACIFIC NORTHWEST—BUSY HIGH RISK OB/GYN PRACTICE. Join well-established, 25-person multispecialty group in Tacoma. Two blocks from Tertiary Center; perform micro and laser surgery, laparoscopy, colposcopy; initial income guarantee; generous benefit package; partnership potential. For detailed fact sheet, contact The Friedrich Group, Inc, 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 547-7850 or (206) 842-5248.

CALIFORNIA—BEAUTIFUL CENTRAL COAST AREA. Nine man, multispecialty group with focus on primary care, seeks a BC/BE Family Practice physician, with preference given to those who include obstetrics. Location in a major rural growth area demands that we recruit to service increased patient volumes. Be prepared to step into an active practice with group conveniences and rewards. Ocean and mountains are an added plus. Excellent salary/fringe benefit package leading to partnership buy-in opportunity. Telephone inquiries welcomed and/or address CV to Valley Medical Group, Patrick M. Quigley, Sr, Administrator, 136 N. Third St, Lompoc, CA 93436; (805) 736-1253.

SAN FRANCISCO, CALIFORNIA. Exciting ground floor opportunities for expanding medical clinics. Interests must be in the areas of physical medicine and rehabilitation. Excellent starting salary and benefits. For consideration, please send CV to Bryce Martin, care of The Orthopaedic Rehabilitation Institute, 181 N. Hudson Ave, Pasadena, CA 91101. Mr Martin may be contacted at (818) 795-9524.

NEUROLOGIST/PACIFIC NORTHWEST. Purchase, for a minimal cost, practice of a Neurologist in Tacoma, Washington, who is retiring soon because of health. He sees approximately 800 new patients a year, and EEG, EMG and evoked potentials can be done in office. CT and MRI testing available. For further information, send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free (800) 626-1590.

GERIATRICS/PACIFIC NORTHWEST. The director of the Geriatrics Unit at our 155-bed hospital in Tacoma, Washington, is seeking an associate who possesses a fellowship or training in Geriatrics. For more information about this opportunity, send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free (800) 626-1590.

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Washington State
Medical Association

1987
Annual Meeting

September 17-20

Tacoma Sheraton

Tacoma,
Washington

THE PACE QUICKENS VALUES ENDURE

WSMA

The Pace Quickens, Values Endure:

WSMA 1987 Annual Meeting At A Glance

Tacoma Sheraton, Tacoma, Washington

Thursday, September 17, 1987

7:00 a.m.	Executive Committee Meeting/ Breakfast	**S** - Executive Board Room
8:00 a.m.	COFFEE – Outside Ballroom (House of Delegates and Registration)	
8:00 a.m.	Registration Opens	**S** - Ballroom Foyer
9:30 a.m.	Board of Trustees Meeting	**S** - South/ Center
Noon	Board of Trustees Luncheon	**S** - South Center
1:30 p.m.	House of Delegates (Opening Session)	**S** - Tacoma Ballroom
3:00 p.m.	COFFEE – Outside Ballroom	**S** - Ballroom
5:00 p.m.	WAFP Caucus Reception	**S** - Pavilion Board Room
6:00 p.m.	HMSS Dinner Meeting	**S** - South/ Center
6:30 p.m.	WSPIE Reception/Dinner Subscribers Advisory Committee	**S** - North

Friday, September 18, 1987

All Day	View Exhibits	**S** - Pavilion
7:00 a.m.	COFFEE	**S** - Pavilion
7:00 a.m.	Registration	**S** - Pavilion
7:00 a.m.	Orthopedics Breakfast	**S** - South
7:30 a.m.	Reference Committees Orientation Breakfast	**S** - Executive Board Room
7:30 a.m.	ACP Breakfast #1 – "Meet the Professor" – Noncardiac Chest Pain	**HI** - Wallowa
7:30 a.m.	ACP Breakfast #2 – "Meet the Professor" – Refresher On The Treatment of Rheumatoid Arthritis	**HI** - Echo
8:00 a.m.	"Medicare: Survival in Troubled Waters – Responding to the Challenge"	**HI** - Private Dining
8:30 a.m.	Reference Committee A	**S** - Ballroom 1
8:30 a.m.	Reference Committee B	**S** - Ballroom 2
8:30 a.m.	Reference Committee C	**S** - Ballroom 3
8:30 a.m.	Reference Committee D	**S** - Ballroom 4
8:30 a.m.	American College of Physicians – Internal Medicine	**HI** - Olympian
8:45 a.m.	Washington State Society of Internal Medicine	**HI** - Wanderer
10:00 a.m.	COFFEE	**HI** - Ballroom Foyer
10:00 a.m.	COFFEE	**S** - Pavilion
Noon	ACP/WSSIM Luncheon	**HI** - Wallowa/ Echo
Noon	Physician/Auxiliary Luncheon	**S** - Pavilion
1:00 p.m.	Psychiatry	**HI** - Conf. I
1:00 p.m.	Emergency Medicine	**HI** - Private Dining
1:00 p.m.	Allergy	**S** - North
1:00 p.m.	WSPIA/WSPIE Policyholders Meeting	**S** - South/ Center
3:00 p.m.	COFFEE	**S** - Pavilion
3:00 p.m.	COFFEE	**HI** - Ballroom Foyer
5:00 p.m.	UW Alumni Reception	**S** - Rotunda
5:00 p.m.	ACP Reception	**HI** - Wallowa
6:00 p.m.	WACEP Board of Directors Dinner/Meeting	**HI** - Conf. II
6:00 p.m.	Allergy Dinner	**S** - S 514
6:30 p.m.	President's Reception and Dinner	**S** - Tacoma Ballroom

Saturday, September 19, 1987

All Day	View Exhibits	**S** - Pavilion
7:00 a.m.	COFFEE	**S** - Pavilion
7:00 a.m.	Registration Continues	**S** - Pavilion
7:00 a.m.	County Medical Society Caucus Breakfasts	**S** - South/ North/Center
7:00 a.m.	Past Presidents' Breakfast	**S** - Executive Board Room
7:00 a.m.	AMA Delegation Breakfast	**S** - Rose
7:00 a.m.	Early Bird Christian Breakfast	**S** - 514
7:30 a.m.	ACP Breakfast #3 – "Meet the Professor" – How to Manage Ventilator	**HI** - Private Dining
7:30 a.m.	ACP Breakfast #4 – "Meet the Professor" – Abnormal Liver Function Tests in the Asymptomatic Patient	**HI** - Echo
8:00 a.m.	Risk Management	**HI** - Wallowa
8:30 a.m.	American College of Physicians – Internal Medicine	**HI** - Wanderer
8:30 a.m.	Washington State Society of Medical Assistants	**HI** - Board Room
9:00 a.m.	Ophthalmology	**HI** - Olympian
9:00 a.m.	Psychiatry	**HI** - Conf. I
9:00 a.m.	Pediatrics	**MB**
9:00 a.m.	House of Delegates	**S** - Tacoma Ballroom
10:00 a.m.	COFFEE	**S** - Pavilion
10:00 a.m.	COFFEE	**HI** - Ballroom Foyer
11:00 a.m.	Ophthalmology Luncheon	**HI** - Private Dining
Noon	Washington State Society of Medical Assistants Luncheon	**HI** - Board Room
Noon	WAMPAC Luncheon	**S** - Pavilion
Noon	Risk Management Luncheon	**HI** - Echo
Noon	Psychiatry Luncheon	**HI** - Conf. II
Noon	Pediatrics Luncheon	**MB**
1:30 p.m	House of Delegates Reconvenes	**S** - Tacoma Ballroom
2:00 p.m.	Association of Senior Physicians of Washington Meeting	**S** - South/ Center
2:00 p.m.	WAMPAC Board of Directors	**S** - North
3:00 p.m.	COFFEE	**S** - Pavilion
3:00 p.m	COFFEE	**HI** - Ballroom Foyer
6:30 p.m.	New Presidents' Reception	**S** - Pavilion

Sunday, September 20, 1987

7:00 a.m.	County Medical Society Caucus Breakfasts	**S** - South/ North/Center
9:00 a.m.	House of Delegates	**S** - Tacoma Ballroom

Key for Locations:
Sheraton: **S**
Holiday Inn: **HI**
Mary Bridge Children's Hospital: **MB**

Shuttle service is available between the Sheraton and Holiday Inn.

For additional information, contact the WSMA office: 1-800-552-0612 or (206) 441-9762.

(Continued from Page 244)

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

SOUTHERN CALIFORNIA—Family Practice, Orthopedic Surgeon, OB/GYN. Private practice opportunities available. For details, call E. Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

NEVADA—FAMILY PRACTICE OR INTERNISTS for salaried positions with opportunities to own a portion of the practice. Located in the beautiful Sparks/Reno area. For details, call E. Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

PACIFIC NORTHWEST—EXPANDING PRACTICE SEEKS OB/GYN. Ground floor opportunity with BC/BE women. Diverse urban clientele, affiliation with major hospital, first year income guarantee, new family-centered delivery facility, malpractice, other benefits, and partnership potential. For detailed fact sheet, contact The Friedrich Group, 9284 Ferncliff, NE, Bainbridge Island, WA 98110; (206) 547-7850 or (206) 842-5248.

OCCUPATIONAL MEDICINE PHYSICIAN, SAN FRANCISCO BAY AREA. $45,117 per year. Immediate opening in three-physician Naval Occupational Medicine division, NAS, Alameda, California. Duties include pre-employment and surveillance examinations, treatment of occupational illnesses and injuries, and health hazard evaluations. Active industrial hygiene support. Must be a US citizen. EOE. For information call, (415) 633-6373.

FAMILY PRACTITIONER. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks a Family Practitioner for full-time work. Competitive salary, excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

COLON RECTAL SURGEON/SOUTHERN CALIFORNIA. The only Colon Rectal Surgeon on active staff at our 236-bed hospital in the western San Fernando Valley is retiring and another is needed. Send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free (800) 626-1590.

FAMILY PRACTICE PHYSICIAN, BC/BE. Scenic northwest. Immediate opening. System of four primary care community clinics. Full-scope family practice, new facilities, excellent salary and fringes, terrific staff. EOE. Send résumés to Dr Richard Witt, Medical Director, Community Health Care Delivery System, 1702 Tacoma Ave S., Tacoma, WA 98402-1709.

PATHOLOGIST. CP/AP, BC/BE, part-time, possibly becoming full-time. CV and references. Reply to Number 48, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA, SAN FRANCISCO BAY AREA. Major HMO seeking BC/BE Emergency Physician to join staff of active Emergency Department in large, urban, academically-oriented medical center. Competitive salary, outstanding fringe benefits, and shareholdership are among the many advantages of joining Kaiser Permanente, the nation's leading HMO. Please address all inquiries to William Barnaby, MD, Emergency Department, Kaiser Permanente Medical Center, 280 W. MacArthur Blvd, Oakland, CA 94611.

PHYSICIANS WANTED

SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join established, progressive, six-physician group practice in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Larry Casalino, MD, 225 S. Cabrillo Hwy, 100A, Half Moon Bay, CA 94019.

OB/GYN. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an OB/GYN to join the two currently on staff. Competitive salary, excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

WASHINGTON, OREGON. Practice opportunities in urgent care and emergency department settings throughout the northwest. Malpractice provided in most locations. Competitive salaries. Recreational activities abound. Write or call L. Poschman, Northwest Emergency Physicians, 11808 Northup Way, Ste 110, Bellevue, WA 98005; (206) 828-6799.

INTERNIST BC/BE—to be second Internist in a satellite of a 36-physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural and educational opportunities. Send CV to Search Committee, 55 W. Tietan, Walla Walla, WA 99362.

THE WALLA WALLA CLINIC, a 36-physician multispecialty clinic, is seeking a second physician to staff an established and growing walk-in Immediate Care Center. Excellent benefit package in a beautiful pacific northwest community with excellent recreational, cultural and educational opportunities. Send CV to James Mercer, MD, 55 W. Tietan, Walla Walla, WA 99362.

WASHINGTON/PUGET SOUND. BC/BE General Internist and Family Practice (OB) positions open in large multispecialty group one block from major hospital. Located in Puget Sound, a short distance to the mountains, and access to three major universities afford our physicians a high-quality life-style and academia. Excellent practice opportunity with good starting salary and full range of benefits. Please reply with CV to Dr William Brand, President, PO Box 5467, Tacoma, WA 98405; (206) 627-9151.

EXCELLENT TEXAS OPPORTUNITIES. ENT, Family Practitioner, General Practitioner, General Surgeon, Internal Medicine, OB/GYN, Ophthalmologist, Oncologist, Pediatrician, Radiation Oncologist, to practice in one of several lake area communities, in the beautiful Piney Woods area of east Texas. Excellent quality of life, first year guarantee, etc. Other Texas opportunities available also. Reply with CV to Medical Support Services, Armando L. Frezza, 11509 Quarter Horse Trail, Austin, TX 78750; (512) 331-4164.

VICE PRESIDENT MEDICAL SERVICES. Offers challenging opportunity to systems oriented physician for Prepaid Health Plan and fee-for-service medical center(s). Excellent salary and fringe benefits. Requires California medical license; one year of formal training in health administration or two years experience in medical care management and proficiency in primary clinical care. Please submit CV to James M. Clayton, CEO, FHFA, PO Box 30051, San Jose, CA 95156-9985. EOE.

INTERNAL MEDICINE. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an Internist for full-time work. Competitive salary, excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

CARDIOLOGIST, INVASIVE. 160-physician, multispecialty, prepaid group located in the San Francisco bay area wishes to add another Cardiologist/Internist. Practice includes large volume of referrals for invasive procedures. Doppler-echo skills required. University affiliation available. Please contact Larry Lawrence, MD, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119.

PHYSICIANS WANTED

WASHINGTON—OB/GYN, Family Practice, Internal Medicine, Endocrinologist, Pulmonary Specialist, Orthopedic Surgeon. Private practice openings with groups, established physicians or solo practices in and near SEATTLE. For details, call E. Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

LOS ANGELES, CALIFORNIA. Exciting opportunity for a BC/BE Physiatrist. Excellent starting salary and benefits. For consideration, please send CV to Bryce Martin, care of The Orthopaedic Rehabilitation Institute, 181 N. Hudson Ave, Pasadena, CA 91101. Mr Martin may be contacted at (818) 795-9524.

WYOMING, CALIFORNIA, TEXAS—Cardiologist. Invasive Cardiologist for Wyoming and Texas positions with established physicians. Noninvasive Cardiologist for southern California or someone willing to travel 25 miles to cath lab. Excellent situations. For details, call E. Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

CALIFORNIA, SAN FRANCISCO. Excellent opportunity for well-qualified, full-time Emergency Physician. Board eligible/certified EM, IM, Surg, FP. Exceptional salary and benefits package. Send letter of interest and CV to Daniel Matulich, MD, Director, Emergency Services, French Hospital, 4131 Geary Blvd, San Francisco, CA 94118.

ONCE IN A LIFETIME OPPORTUNITY. Large general practice and clinic for sale by General Practitioner preparing for retirement. Practice is part of a progressive and rapidly expanding community located in central Minnesota near excellent winter and summer recreation. Current clinic grosses over $500,000 annually, is expandable and equipped with surgery, x-ray, lab and set up for pharmacy. Fee for service and growing! Malpractice insurance not a serious problem. Computerized; excellent staff. Great potential for aggressive GPs, FPs, Internists or Surgeons. Excellent hospital one mile. Contact Janet K. (612) 251-9191.

NEPHROLOGIST/INTERNIST. Opening available in 160 plus physician group. Join additional Nephrologist/Internist in a busy and fulfilling HMO practice in the San Francisco bay area. Excellent working conditions. Ample opportunities for house staff teaching, clinical faculty appointment, cooperative group participation. Competitive salary. Superb benefit package. Reply with CV to Joseph Mason, MD, Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119. An Equal Opportunity/Affirmative Action Employer.

RESEARCH ASSISTANT. Master's Degree in Biological Applied Science or related field; two years experience in cardiology research; familiarity with physiology and pathology of the heart, the effect of drugs on heart function, quantification of two-dimensional computerized echocardiographic images, retroperfusion and digital angiography required. $30,180 per year. Job site: Los Angeles. Send this ad and a résumé to Job # SK 6057, PO Box 9560, Sacramento, CA 95823-0560 not later than September 7, 1987.

SAN JOSE (SANTA CLARA COUNTY) BC/BE FAMILY PRACTITIONER for rapidly expanding staff model HMO. Spanish speaking helpful. Excellent salary and fringe benefits. Clinic practice part-time/full-time, evenings/weekends. Contact: Medical Director, PO Box 30051, San Jose, CA 95156-9985; (408) 262-7944.

PHYSICIAN, PART-TIME, OUTPATIENT CLINIC. Substance abuse treatment, General Medicine. Supervision of physician assistants, administrative tasks; large multidisciplinary team. Training provided, ongoing education available. Call Susan Sky, Oakland, California, (415) 533-0800, Monday thru Friday, 10:00 AM-Noon.

(Continued on Page 250)

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PHYSICIANS WANTED

NUTRITION/WELLNESS

Primary-care physician wanted to associate with GP in busy nutritional/wellness oriented medical practice in southern California. Experience in this type of practice is preferred, but will instruct. Potential for partnership. Excellent opportunity for right person. Send CV to John LaMont, MD, 909 Electric Ave, Ste 212, Seal Beach, CA 90740, or call (213) 493-4526, ask for Sally.

ATTENTION WANTED

INTERNIST, ENDOCRINOLOGIST, BE. Trained at UCSF. Prior outpatient Primary Care experience. Desires position consisting of General Internal Medicine and specialty in San Francisco bay area. Reply to Number 49, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1988, date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 9-12, 1987, Beaver Run, Breckenridge.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1987, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1988, date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1988, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1988, date and place to be announced.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 9-11, 1987, Marriott Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 17-20, 1987, Sheraton, Tacoma.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1988, date and place to be announced.

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Rocephin® IV·IM

ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

MICROBIOLOGY The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta lactamases, both penicillinases and cephalosporinases, of gram-negative and gram positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

GRAM-NEGATIVE AEROBES Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, e g penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

GRAM POSITIVE AEROBES Staphylococcus aureus (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note methicillin resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

GRAM-NEGATIVE AEROBES Citrobacter freundii, Citrobacter diversus, Providencia species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*

ANAEROBES Bacteroides species, *Clostridium* species (Note most strains of *C difficile* are resistant)

SUSCEPTIBILITY TESTING Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW, Kirby WMM Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45 493-496, 1966, Standardized Disk Susceptibility Test, *Federal Register* 39 19182-19184 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

DILUTION TECHNIQUES Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g, urine), in which high antibiotic levels are attained

E coli ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

PROPHYLAXIS The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

ROCEPHIN® (ceftriaxone sodium/Roche)

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

PRECAUTIONS *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis

DOSAGE AND ADMINISTRATION Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g , dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

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* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

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Please see adjacent page for summary of product information.

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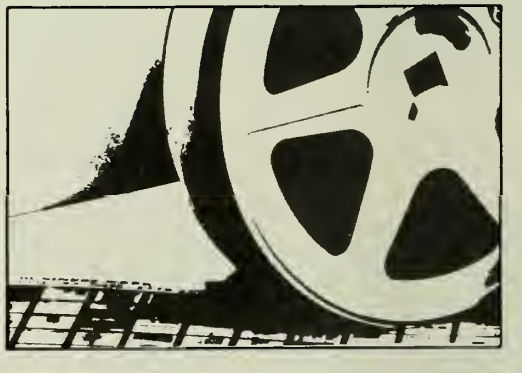

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This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
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WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

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Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
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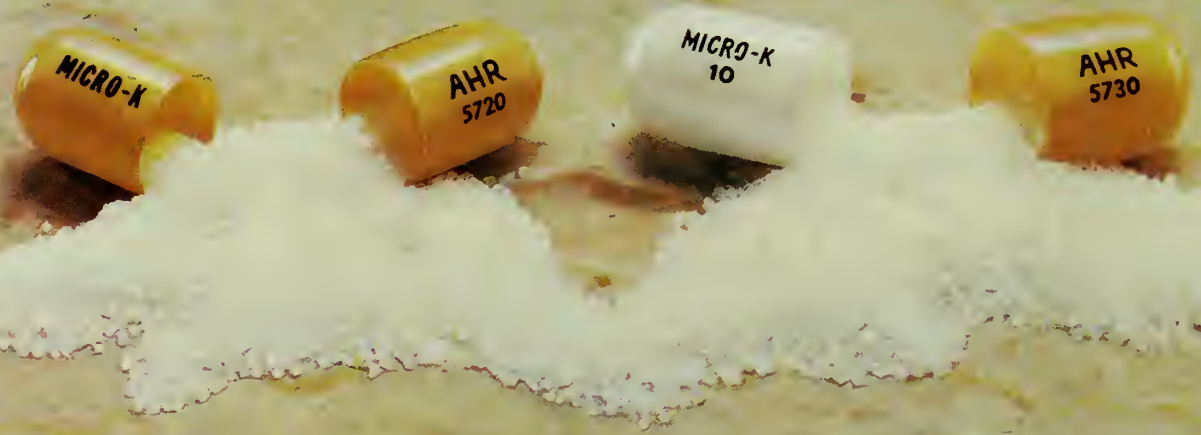

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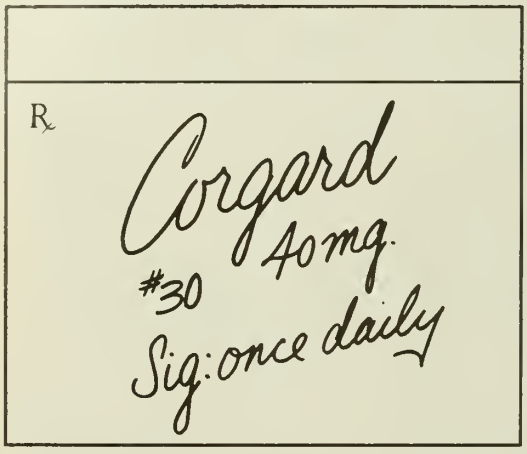

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CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

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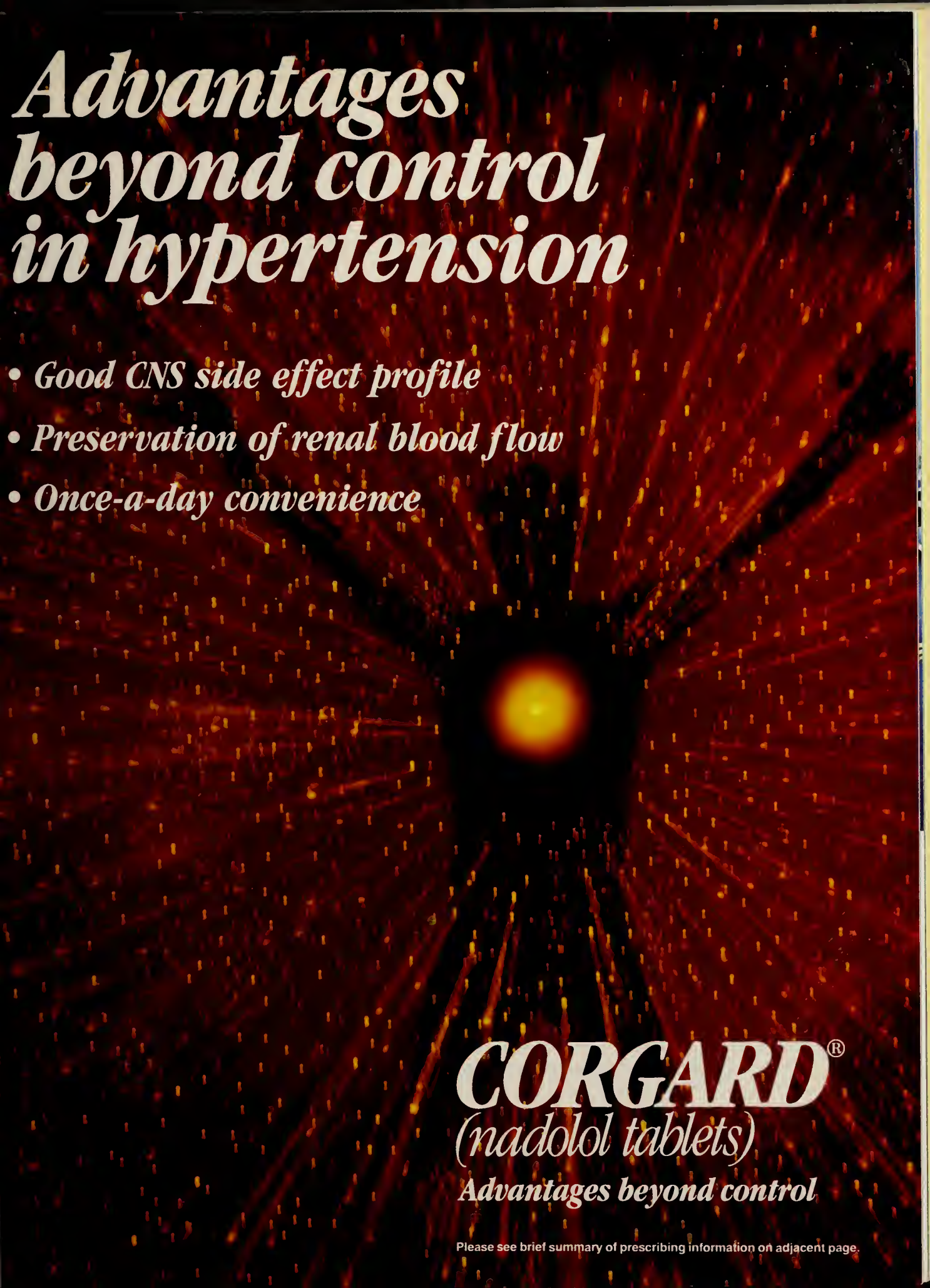
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The Western Journal of Medicine

SINCE 1902

ISSN 0093-0415

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The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $4.50 (which includes postage and handling). Address all subscription communications to:

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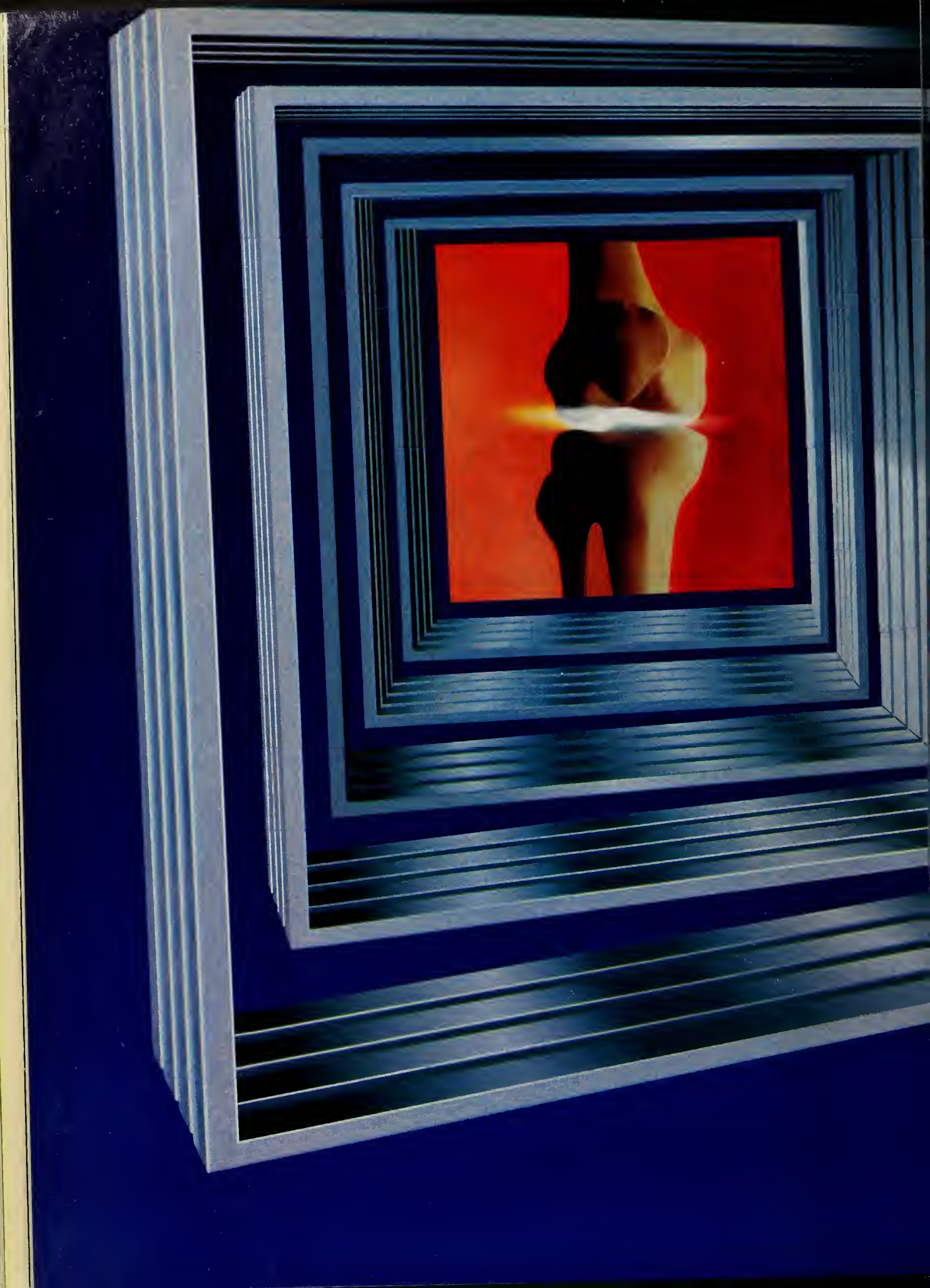

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Inflammation is usually a factor in the pain of osteoarthritis. There's ample evidence of this,[1-5] and it may explain why some patients require higher, anti-inflammatory doses of MOTRIN Tablets (ibuprofen).

Studies and experience have shown that at dosages up to 1200 mg/day, ibuprofen is primarily analgesic. Anti-inflammatory activity is added to effective analgesia in patients taking higher dosages of MOTRIN.[6-8]

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Extra-strength MOTRIN 800 mg tablets are a more convenient way to provide the higher doses required to maintain anti-inflammatory activity.

Just one 800 mg tablet t.i.d. provides 2400 mg/day for osteoarthritis patients who require higher doses of MOTRIN. If necessary, patients can take one tablet q.i.d. Doses above 3200 mg/day are not recommended. The lowest effective dosage should be used. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin.

Please turn the page for references and a brief summary of prescribing information.

A stronger reason to prescribe MOTRIN in osteoarthritis

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For the inflammation and the pain of osteoarthritis

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A stronger reason to prescribe MOTRIN.

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MOTRIN® Tablets
(ibuprofen)

CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship**

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown**

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

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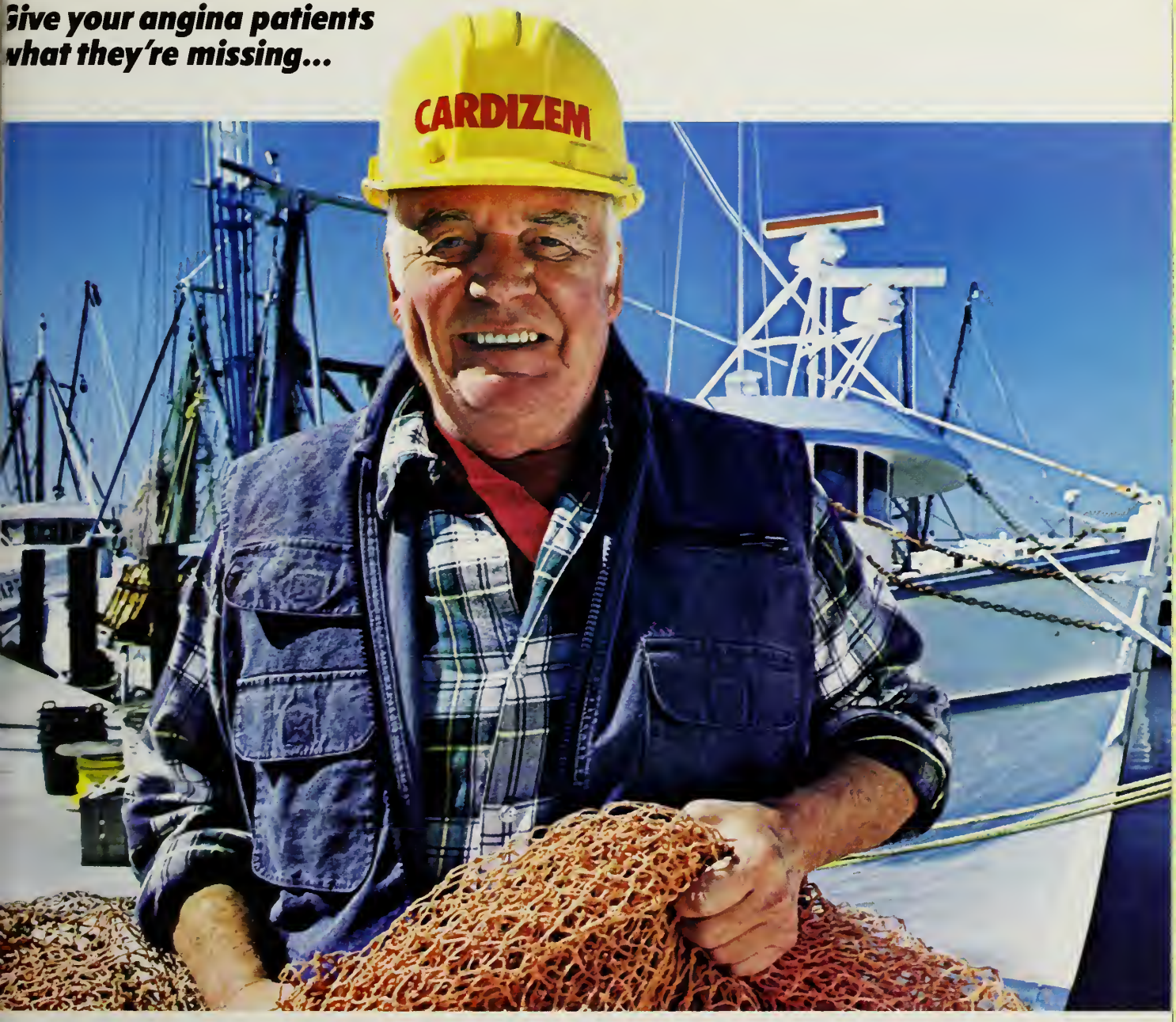

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- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

90 mg NEW 120 mg GREATER DOSAGE FLEXIBILITY

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.

CARDIZEM® FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

diltiazem HCl/Marion

60 mg tid or qid

Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg, and 120 mg Tablets

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS
General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.*
Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*
Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.
Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*
Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*
Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.
In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.
The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. *Issued 9/86*

See complete Professional Use Information before prescribing.

References: ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983; 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984;24(Dec):150-159.* ***3.*** *Johnston DL, Lesoway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50(Sept):94-116.*

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1403E7

(Continued from Page 262)

340 **Wright's Law Is Right On**
GARY GORLICK, MD, MPH

340 **Insects in the Operating Room**
RONALD A. SHERMAN, MD; JAMES SPIEGEL, MD, and REGINA F. GANDOUR, MD

341 **Asthma and Urticaria After Hepatitis B Vaccination**
GHANSHYAM LOHIYA, MD

TOPICS IN PRIMARY CARE MEDICINE

342 **Reflex Sympathetic Dystrophy Syndrome—Diagnosis and Management**
DAVID L. SMITH, MD, and STEPHEN M. CAMPBELL, MD
From the Ambulatory Care and Medical Service, Veterans Administration Medical Center, and the Division of General Medicine, Section of Arthritis and Rheumatic Disease, Oregon Health Sciences University School of Medicine, Portland.

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346 **How Physicians Can Improve Patients' Participation and Maintenance in Self-Care**
LAWRENCE W. GREEN, DrPH
From the Center for Health Promotion Research and Development, University of Texas Health Science Center at Houston.

SPECIAL ARTICLE

350 **Private Financing Options for Long-term Care**
BARBARA L. BRODY, MPH; HAROLD J. SIMON, MD, PhD, and DENNIS E. SMALLWOOD, PhD
From the Departments of Community and Family Medicine and of Economics, University of California, San Diego, School of Medicine, La Jolla.

RADIOLOGIC CASE

357 **Pelvic Fullness, Urgency and Frequency Following Lymphadenectomy**
RENEE A. SPIEGEL, MS; SAMUEL J. HESSEL, MD; EDWARD R. KATZ, MD, and JONATHAN M. LEVY, MD
From the University of Arizona College of Medicine, Tucson, and the Departments of Radiology and Urologic Surgery, Scottsdale Memorial Hospital, Scottsdale, Arizona.

INFORMATION

359 **Endoscopic Sclerotherapy for Esophageal Varices**
HARVEY S. YOUNG, MD
From the Department of Medicine, Division of Gastroenterology, Stanford University School of Medicine, Stanford, California.

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278 **Books Received**

284 **Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming**

365 **Subscription Information**

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384 **Western State Medical Associations' Meetings**

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

San Francisco
Department of Public Health

National Conference

AIDS: Health Department Leadership And Community Response

November 4-7, 1987: San Francisco, CA

Program focus: Developing a comprehensive system for AIDS education, prevention and care.

Presentations will address the central role of the local health department in cooperation with community agencies to: plan, organize, coordinate and allocate resources to assure the quality of the community's overall AIDS program.

Session Topics

Public Education

Community-wide involvement and planning

Financing AIDS programs

Health department/school system coordination

Hospital and community-based care and support services

Antibody testing

Mental health and substance abuse services

Jail health services

Maternal/child health services

Epidemiology studies

Minority community issues

Legal, ethical and policy issues

Conference participants: State and local public health administrators; health program managers, educators and planners; healthcare and hospital administrators; mental health and substance abuse program managers; providers of AIDS care (including physicians, nurses and home care); community-based organizations; public officials and staff.

Conference fees: $125 (before September 15); $175 (after September 15) 20% discount for four or more registrants from same agency or organization.

Limited number accepted in the following registration categories:
Community-based agency staff: $50
Individuals with special circumstances: $50
Persons with AIDS/ARC: Complimentary
CE Credit in process: $50 extra fee

Conference registration contact:
SFDPH AIDS Conference, c/o KCMS
207 Day Street, San Francisco, CA 94131

CARAFATE®
(sucralfate)

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that the simultaneous administration of CARAFATE with tetracycline, phenytoin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. The clinical significance of these animal studies is yet to be defined.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related tumorigenicity was found in chronic oral toxicity studies of 24 months' duration conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies have not been conducted.

Pregnancy: Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients, adverse effects were reported in 121 (4.7%). Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm pink tablets are supplied in bottles of 100 and in Unit Dose Identification Paks of 100. The tablets are embossed with MARION/1712. Issued 3/84

References:

1. Korman MG, Shaw RG, Hansky J, et al: *Gastroenterology* 80:1451-1453, 1981.
2. Korman MG, Hansky J, Merrett AC, et al: *Dig Dis Sci* 27:712-715, 1982.
3. Brandstaetter G, Kratochvil P: *Am J Med* 79(suppl 2C):36-38, 1985.
4. Marks IN, Wright JP, Gilinsky NH, et al: *J Clin Gastroenterol* 8:419-423, 1986.
5. Lam SK, Hui WM, Lau WY, et al: *Gastroenterology* 92:1193-1201, 1987.

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1594H7

Ulcer therapy that won't yield, even to smoking

What do you do for duodenal ulcer patients who should stop smoking, but won't? Both cimetidine[1] and ranitidine[2] have been shown less effective in smokers than nonsmokers.

Choose CARAFATE® (sucralfate/Marion). Two recent studies show Carafate to be as effective in smokers as nonsmokers.[3,4] A difference further illustrated in a 283-patient study comparing sucralfate to cimetidine[5]:

Ulcer healing rates:
(at four weeks of therapy)[5]

Sucralfate:	
All patients	79.4%
Smokers	81.6%*
Cimetidine:	
All patients	76.3%
Smokers	62.5%

*Significantly greater than cimetidine smoker group ($P<.05$).

Carafate has a unique, nonsystemic mode of action that enhances the body's own ulcer healing ability and protects the damaged mucosa from further injury.

When your ulcer patient is a smoker, prescribe the ulcer medication that won't go up in smoke: safe, nonsystemic Carafate.

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Please see adjoining page for references and brief summary of prescribing information.

1594H7

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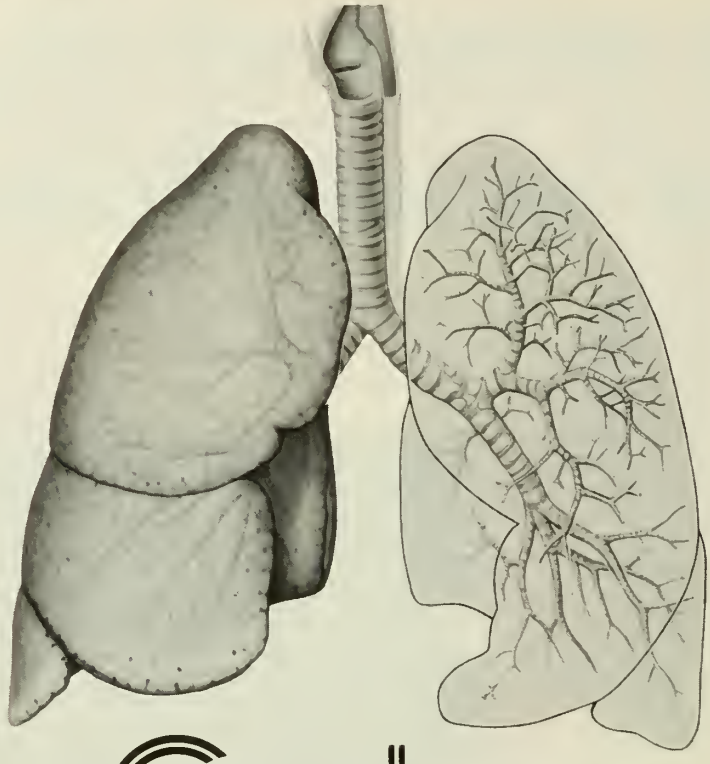

Ceclor®
cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae, Streptococcus pneumoniae
(ampicillin-susceptible and ampicillin-resistant)

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins.

Warnings:
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

[072886R]

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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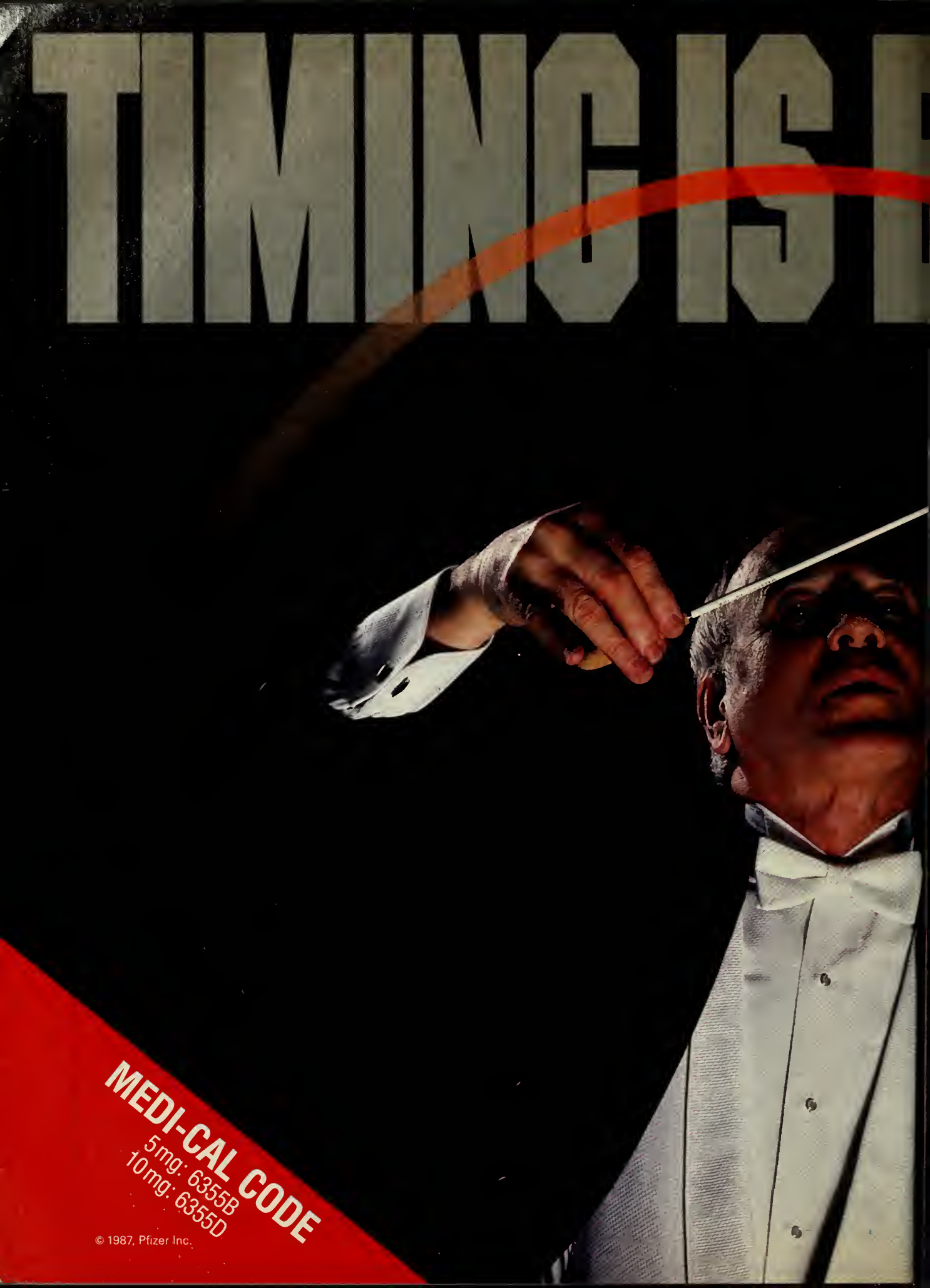

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VERYTHING

Effective control time and time again[1]

Effective control of fasting and postprandial glucose—patient after patient, meal after meal, year after year.

Insulin when it's needed

Insulin levels are rapidly elevated in response to a meal, then return promptly to basal levels after the meal challenge subsides.

Timed to minimize risks

Rapidly metabolized and excreted, with an excellent safety profile.[1] As with all sulfonylureas, hypoglycemia may occur.

In concert with diet in non-insulin-dependent diabetes mellitus

Glucotrol®

(glipizide) 5-mg and 10-mg Scored Tablets

SYNCHRONIZED SULFONYLUREA THERAPY

Please see brief summary of Glucotrol® (glipizide) prescribing information on next page.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

Reference
1. Sachs R, Frank M, Fishman SK. Overview of clinical experience with glipizide. In *Glipizide: A Worldwide Review*. Princeton, NJ: Excerpta Medica, 1984, pp 163-172

GLUCOTROL® (glipizide) Tablets
Brief Summary of Prescribing Information
INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.
CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.
SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 19, supp. 2:747-830, 1970).
UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.
Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.
PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.
Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.
Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.
Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.
Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.
Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.
Pregnancy: Pregnancy Category C. GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.
Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.
Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.
Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.
Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas. GLUCOTROL should be discontinued if this occurs.
Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL. If skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.
Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.
Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.
Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.
Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.
OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.
DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL, in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.
Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.
Maximum Dose: The maximum recommended total daily dose is 40 mg.
Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.
HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) 8 bottles of 100, 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) 8 bottles of 100.
CAUTION: Federal law prohibits dispensing without prescription.
More detailed professional information available on request.

ROERIG Pfizer A division of Pfizer Pharmaceuticals New York, New York 10017

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 10, 1987—Edited by W. Maxwell Cowan, Washington University; Eric M. Shooter, Stanford University School of Medicine; Charles F. Stevens, Yale University School of Medicine, and Richard F. Thompson, Stanford University. Annual Reviews Inc, 4139 El Camino Way, PO Box 10139, Palo Alto, CA 94303-0897, 1987. 693 pages, $31.

THE ARTERIAL ANATOMY OF SKIN FLAPS—George C. Cormack, MA, MB, ChB, FRCS (Ed), formerly Department of Anatomy, University of Cambridge, and Fellow of Queens' College, Cambridge, and B. George H. Lamberty, MA, MB, BChir, FRCS, Consultant Plastic Surgeon, Addenbrooke's Hospital, Cambridge, and Associate Lecturer, University of Cambridge. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 442 pages, $195.

ATLAS OF U.S. CANCER MORTALITY AMONG WHITES: 1950-1980—Linda Williams Pickle, PhD, and Thomas J. Mason, PhD, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland; Niel Howard, ORI, Inc, Washington, DC; Robert Hoover, MD, and Joseph F. Fraumeni, Jr, MD, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland. US Department of Health and Human Services, National Institutes of Health, Bethesda, MD 20892, 1987. 184 pages, price not given.

BEDSIDE LOGIC IN DIAGNOSTIC GASTROENTEROLOGY—James Christensen, MD, Professor, Division of Gastroenterology-Hepatology, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 165 pages, $18 (paperback).

CARDIOVASCULAR DISEASE—Volume 1 in A Profile of Health and Disease in America—Wrynn Smith, PhD. Facts On File, 460 Park Ave South, New York, NY 10016, 1987. 121 pages, $35.

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EVALUATING PREVENTIVE CARE—REPORT ON A WORKSHOP—Louise B. Russell, a senior fellow in the Brookings Economic Studies Program, Washington, DC. The Brookings Institution, 1775 Massachusetts Ave, NW, Washington, DC 20036, 1987. 101 pages; $22.95 (cloth), $8.95 (paperback).

THE EXERCISING ADULT—Second Edition—Edited by Robert C. Cantu, MD, Chief, Neurosurgical Service, and Director, Service of Sports Medicine, Emerson Hospital, Concord, Massachusetts. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1987. 285 pages, $29.95.

FLEXNER: 75 YEARS LATER—A CURRENT COMMENTARY ON MEDICAL EDUCATION—Edited by Charles Vevier, PhD, Professor, Department of Psychiatry, UMDNJ-New Jersey Medical School, Newark. University Press of America, 4720 Boston Way, Lanham, MD 20706, 1987. 114 pages, price not given.

FOREIGN TRAVEL & IMMUNIZATION GUIDE—12th Edition—Hans H. Neumann, MD, Director of Preventive Medicine, Department of Health, Yale University School of Medicine, New Haven, Connecticut. Medical Economics Books, Box C-779, Pratt Station, Brooklyn NY 11205-9066, 1987. 80 pages, $12.50 (paperback).

GERIATRIC MEDICINE ANNUAL 1987—Edited by Richard J. Ham, MD, Professor and Distinguished Chair in Geriatric Medicine and Director, Program in Geriatrics, State University of New York, Health Sciences Center at Syracuse, and President-Elect, American Geriatrics Society. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205. 278 pages, $35.95.

HANDBOOK OF GASTROINTESTINAL IMAGING—R. Kristina Gedgaudas-McClees, MD, Associate Professor, Department of Radiology, Emory University School of Medicine, Atlanta. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 257 pages, $49.

HEMATOLOGIC PROBLEMS IN PREGNANCY—Edited by David Z. Kitay, MD, Associate Professor of Obstetrics and Gynecology, University of South Alabama College of Medicine, Mobile. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205-9066, 1987. 408 pages, $39.95 (paperback).

KILL AS FEW PATIENTS AS POSSIBLE—Oscar London, MD, WBD. Ten Speed Press, PO Box 7123, Berkeley, CA 94707, 1987. 102 pages, $7.95 (paperback).

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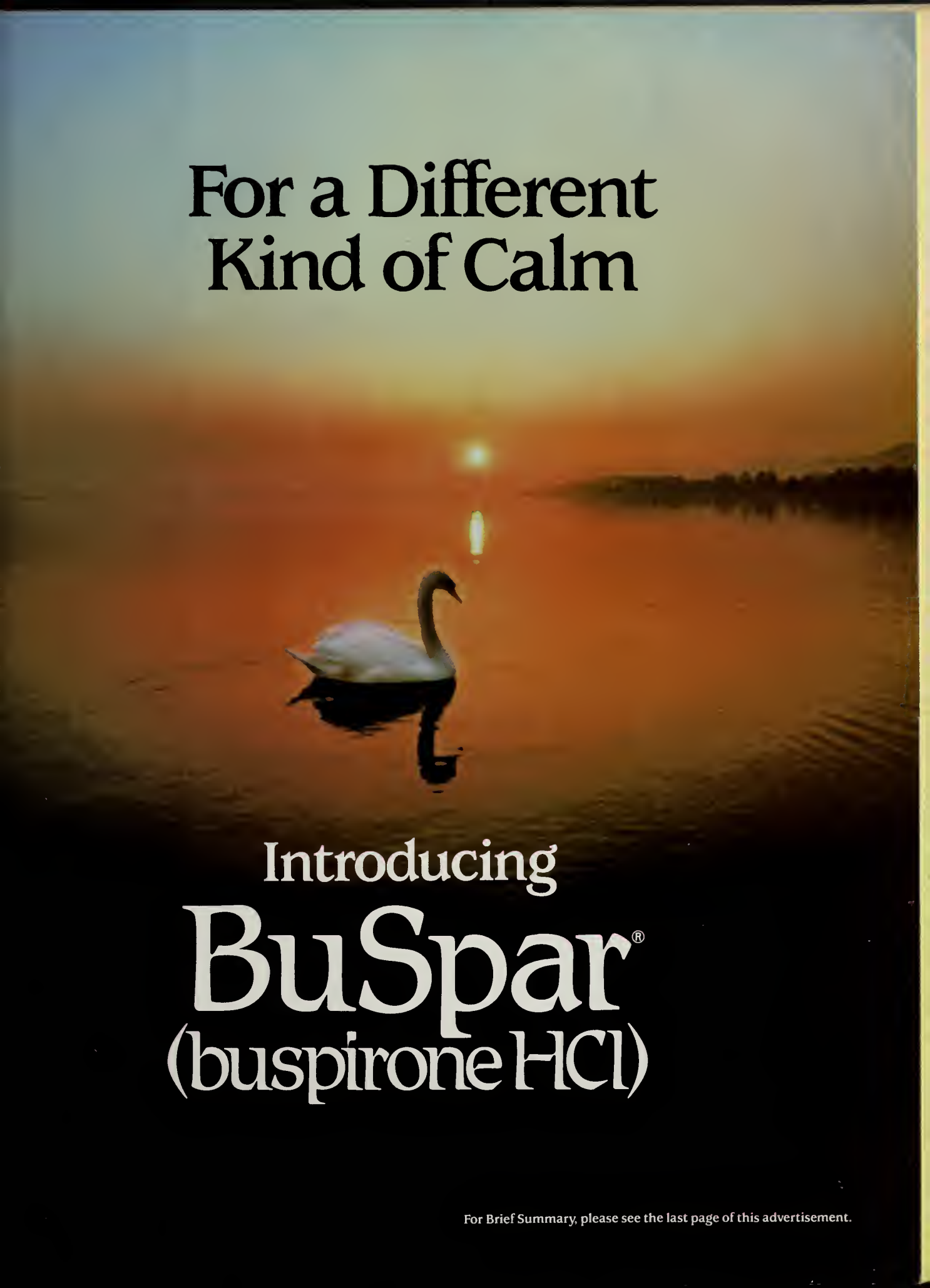
MANUAL OF CATARACT SURGERY—Robert M. Sinskey, MD, Associate Clinical Professor of Ophthalmology, UCLA School of Medicine, Los Angeles, and Medical Director, Southern California Lions' Eye Institute, Santa Monica, and Jay V. Patel, MD, Clinical Instructor of Ophthalmology, UCLA School of Medicine, Los Angeles, and Attending Staff, St John's Hospital, Santa Monica, and Alhambra Community Hospital, Alhambra, California. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 94 pages, $30 (paperback).

For a Different Kind of Calm



Introducing BuSpar® (buspirone HCl)

For Brief Summary, please see the last page of this advertisement.

Mead Johnson
Pharmaceuticals
Introduces

BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

A different kind of calm

BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.[1,2,3]

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.[4,5]

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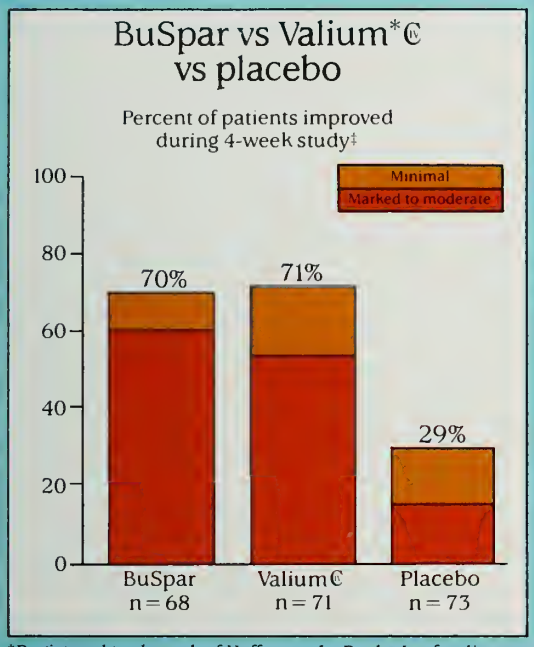
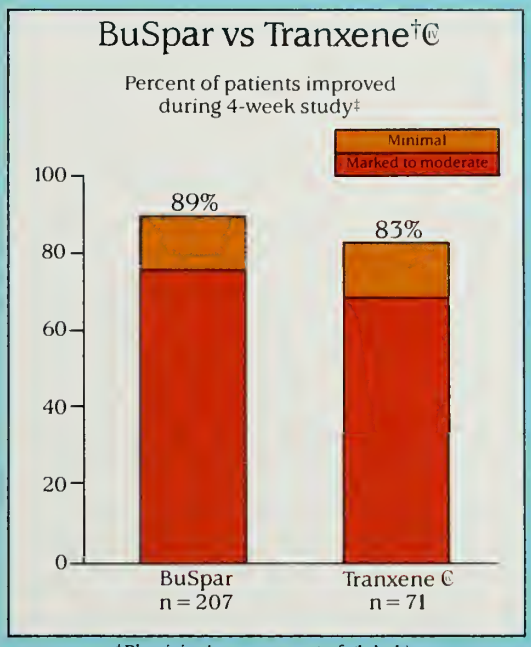
Proven anxiolytic effectiveness over a 4-week course of therapy[6,7]





*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.
‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,* and cardiovascular and gastrointestinal complaints.

*BuSpar is not indicated for the treatment of primary depressive disorder.

For Brief Summary, please see the last page of this advertisement.

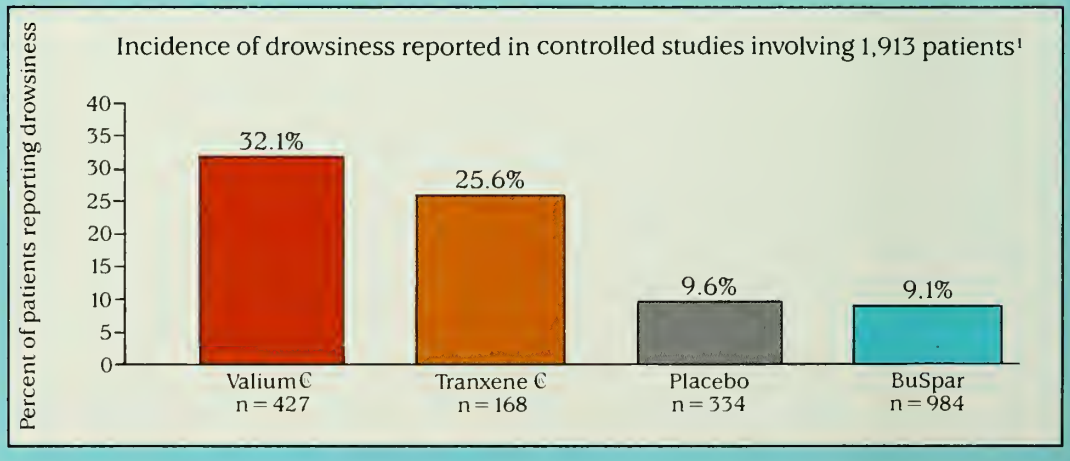
BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

Anxiolytic efficacy without CNS-depressant activity

Incidence of drowsiness no greater than placebo

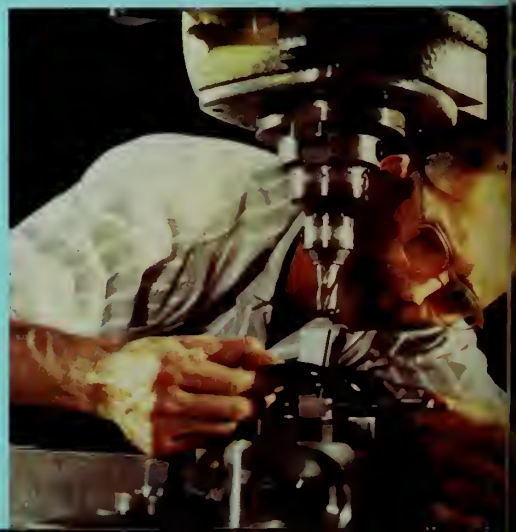
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.[1]



No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.[2]

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.



No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.*[3]

No apparent abuse liability

Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.[4,8]

Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.

BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

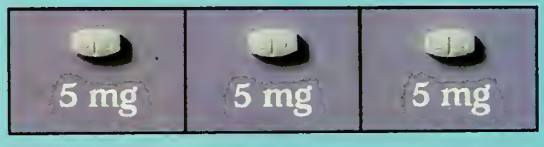
Subtle onset of effect

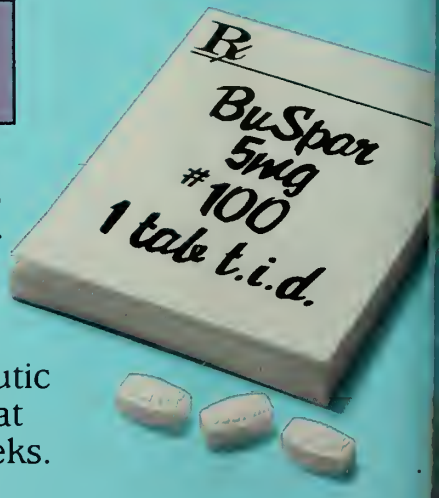
BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1





Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is <u>not</u> a controlled substance.

Patient selection

BuSpar will not block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

If you elect to switch a patient from a benzodiazepine to BuSpar:

1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

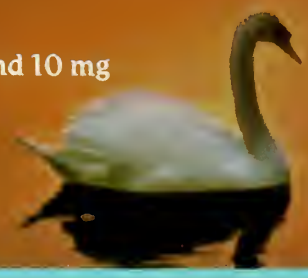
BuSpar...the first choice in anxiolytic therapy when:

- ☑ Treatment requires regular dosing for more than a few days
- ☑ Patient functioning is key to safe and successful treatment
- ☑ The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.

BuSpar® (buspirone HCl)

Tablets
5 mg and 10 mg



For a different kind of calm

CONTRAINDICATIONS:
Hypersensitivity to buspirone.

WARNINGS:
The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:
Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers:
Administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly:
No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%. **CNS:** dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** blurred vision 2%. **Gastrointestinal:** nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** musculoskeletal aches/pains 1%. **Neurological:** numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. **Skin:** skin rash 1%. **Miscellaneous:** headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular:** Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. **Central Nervous System:** Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. **EENT:** Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. **Endocrine:** Rare were galactorrhea and thyroid abnormality. **Gastrointestinal:** Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. **Genitourinary:** Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. **Musculoskeletal:** Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. **Neurological:** Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. **Respiratory:** Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. **Sexual Function:** Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence. **Skin:** Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails. **Clinical Laboratory:** Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia. **Miscellaneous:** Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

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PHARMACEUTICALS
Bristol-Myers U.S. Pharmaceutical
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Evansville, Indiana 47721 U S A

MJL3-4856

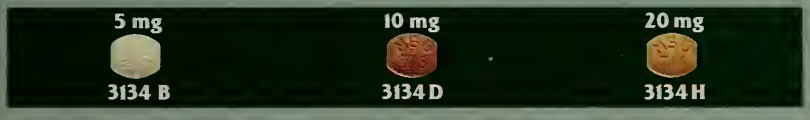
FOR HYPERTENSIVE PATIENTS INTOLERANT OF BETA-BLOCKER THERAPY

CONSIDER

VASOTEC®

(ENALAPRIL MALEATE | MSD)

NOW AVAILABLE ON MEDI-CAL AUGUST 1, 1987



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TIENTS FEEL

Usually No Interference with Physical or Mental Activity

Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC—a fact that may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

Also, certain central effects, such as impairment of memory, nightmares, or depression, have not been characteristic of VASOTEC.

ACE* Inhibition That Favorably Affects Certain Hemodynamic Parameters in Many Patients

VASOTEC has a highly specific mode of action which acts on the renin-angiotensin-aldosterone system—it blocks ACE from converting angiotensin I to angiotensin II, one of the most potent vasoconstrictors known. For many hypertensive patients, VASOTEC favorably affects certain hemodynamic parameters: peripheral arterial resistance is reduced with an increase in cardiac output and no significant change in heart rate; sodium and water retention are also reduced.

VASOTEC is contraindicated in patients who are hypersensitive to this product.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme (ACE) inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC in clinical trials). In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. In using VASOTEC, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and the available data are insufficient to show that VASOTEC does not have a similar risk (see WARNINGS).

Discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

*angiotensin-converting enzyme

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

IT MAY HELP CHANGE THE WAY YOU MANAGE YOUR HYPERTENSIVE PATIENTS

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enatapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and AOVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Oosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See OOSAGE AND AOMINISTRATION in complete Prescribing Information.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose. (See WARNINGS and OOSAGE ANO ADMINISTRATION in complete Prescribing Information.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC® (Enalapril Maleate, MSO) has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to signiticant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses ot 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials or since the drug was marketed include:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Renal: Renal dysfunction, renal failure, oliguria. (See PRECAUTIONS and OOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Other: Oyspnea, muscle cramps, hyperhidrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with faryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% ol patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Dosage and Administration: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg (break the 5-mg tablet) should be used under medical supervision for at least one hour to determine whether excess hypotension will occur. (See WARNINGS and PRECAUTIONS, *Drug Interactions.)*

The recommended initial dose in patients not on diuretics is 5 mg once a day. Oosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Renal Impairment: The usual dose ot enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine ot up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily. For dialysis patients, the initial dose and the dose on dialysis days is 2.5 mg/day. Oosage on nondialysis days should be adjusted depending on blood pressure response.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J6VS12(406R)

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 10—**Recent Advances in Epilepsy.** Hilton Pavilion, Mesa. Sat. Contact: U of A.

October 15—**Current Perspectives: Wellness.** Little America, Flagstaff. Thurs. Contact: ArMA.

November 5-7—**Gynecologic Surgery: Principles, Techniques and Management of Complications.** Hyatt Regency, Scottsdale. Thurs-Sat. Contact: Robin Murray, ACOG, (202) 638-5577, ext 343.

November 13-15—**Bone and Joint Disorders.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Maricopa Medical Center, (602) 267-5361.

November 16-17—**Update on Management of Spina Bifida.** La Posada Resort, Scottsdale. Mon-Tues. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800)-BARROW-1.

January 22-24—**14th Annual Sports Medicine Symposium.** Holiday Inn Metrocenter, Phoenix. Fri-Sun. Contact: ArMA.

February 1-3—**State of the Art 2D/Doppler and Color Flow Imaging.** Sheraton El Conquistador Resort, Tucson. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226

February 4-6—**14th Annual Frontiers in Ophthalmology.** Scottsdale Hilton, Scottsdale. Thurs-Sat. Contact: Campbell Meeting Management for St Luke's Medical Center, (602) 838-6728.

March 2-4—**11th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Secretary, Phoenix OB/GYN Society, (602) 241-1917.

March 6-9—**2nd Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1

March 7-9—**Practical Cardiology for the Family Physician.** La Posada Resort Hotel, Scottsdale. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226.

March 10-12—**15th Annual Symposium: Selected Topics in Ischemic and Hemorrhagic Cerebrovascular Disease.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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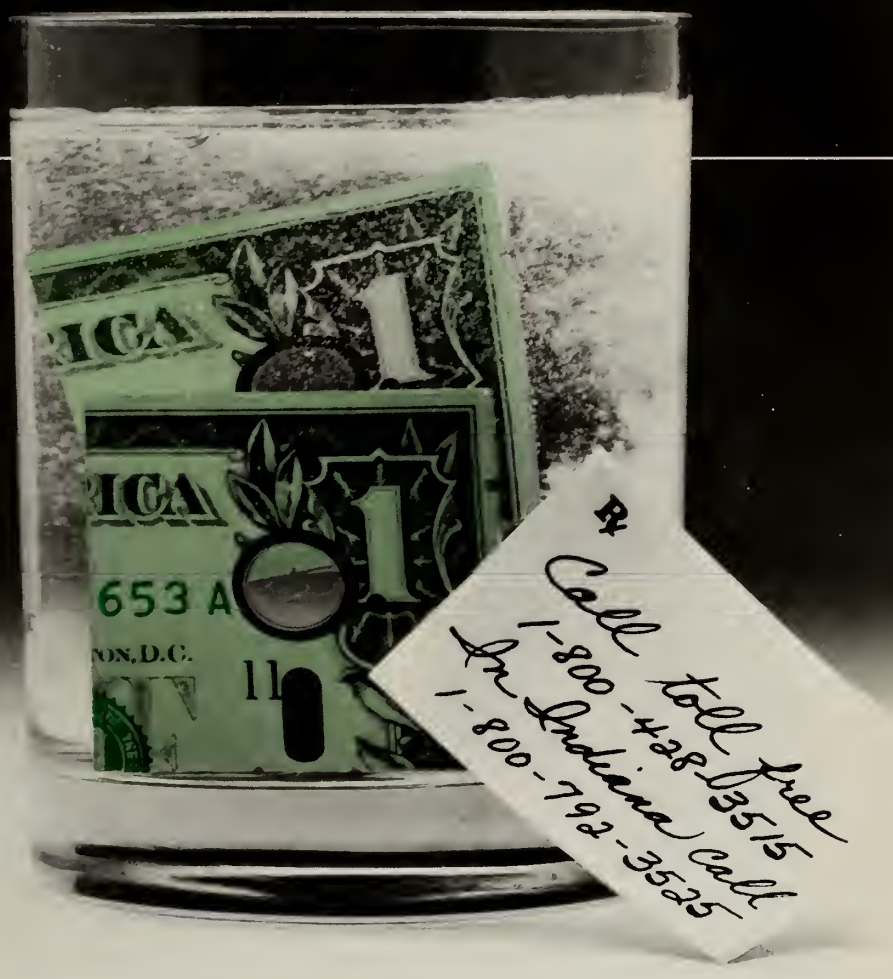

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*

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*

Warnings: ***Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.*** *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*

Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperg·cemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*

Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*

Supplied: ***'Dyazide' is supplied as a red and white capsule in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.***

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

SEPTEMBER 1987, VOL. XLIV, NO. 9

There Are No Shortcuts

Marshall B. Block, M.D.

Several years ago my father called to inform me that he had embarked on a new career following his "retirement" in Florida. He was now "an educator." He then asked me what position I held in the university (this was during my Fellowship days), and I responded that "I was an instructor." "Just an instructor? After how many years of training?" (What he really was thinking was after how many thousands of dollars), "Just an instructor!"

I tried to explain the intricacies of promotion in academic circles but had the feeling that he was just waiting for me to finish before giving me the coup de grace. "I was just made a full professor! What's taking you so long?" I cringed inside. My father who completed just the 8th grade (not even a high school graduate) now a full professor! I quickly recovered. "At which university?" "Well, it isn't a university but a technical school. They hired me to teach the returning Vietnam veterans dental technology. They have 'free' schooling coming their way and the school needed to expand its staff. There is talk that I might even become a Dean!"

There was little I could say but "Congratulations!" Several weeks later, however, the rest of the story unfolded. "How is the Professor?" I asked when I called him. A pause ensued, and my father relayed that he "resigned from the school." It seems they wanted him to drag out the training course over six months in order to obtain the maximum government financing per student possible. My father felt he could teach the recruits all they needed to know in four weeks and wasn't "going to be a party to fraud." So ended my father's short academic career.

The story, however, is a reflection of a bigger problem which we face daily and is detailed in various phrases such as, "there is no free lunch," "quid pro quo," "nothing comes easily," "if it's too good to be true, it probably is,""beware of Romans bearing gifts," etc., etc. No matter how often these phrases are expressed by knowledgeable advisors, be they lawyers, other physicians, accountants, or clergy, we still fall prey to the "easy way out," the shortcut. How often have we been caught taking a chance whether it be financially by not doing due diligence, or medically, by not thinking of all the possibilities when evaluating a difficult problem? It is easy to look at the obvious and avoid the rest, only later to discover the error in such an approach. The "red herring" from our CPC days still haunts us, and we must be constantly on guard to ensure that we take into consideration all factors before arriving at a decision. Computers help in this process, but ultimately we will need to make the final decision and it should be made without haste and with all the facts in place beforehand. ■

Marshall B. Block, M.D., Editor

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

AUGUST 1987, VOL. XLIV, NO. 8

Arizona Medicine is a socioeconomic and scientific journal published monthly by The Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by The Arizona Medical Association.

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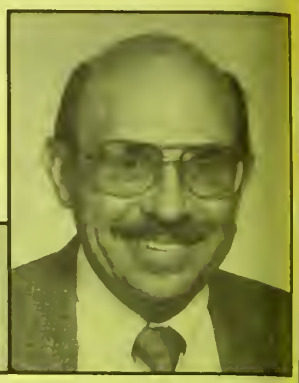
From Our President



Robert S. Hirsch, M.D.

Over a month has passed since the annual meeting of ArMA and there has been considerable activity in several areas of concern. I will address one of them.

The problem of professional liability insurance and the climate that leads to spiraling premium rates has been foremost on all of our minds. When one sees almost daily the anguish of treasured colleagues agonizing over decisions to leave their practices, one must ponder his own professional future with great anxiety.

Obviously, some specialties are more threatened than others, simply because there is such a variability of premium rates. The situation has been addressed from many points of view. Our insurance company, MICA, has a responsibility to be there to provide counsel and coverage when the need arises, and the need seems to be arising more frequently.

While we may argue with the premiums we pay, we must realize that a significant proportion of the liability is of our own making, and is quite avoidable. Our insurance company is unable to defend poor documentation, illegible orders or progress notes, alteration of records, excessive prescriptions for classified drugs, compromised mental function due to substance abuse, failure to respond to patient calls, surly or arrogant attitude, these to mention only a few of the kinds of ammunition that can be given a plaintiff. These failures of action and attitude have been pointed out many times, yet they appear over and over again. They are easily correctable and their correction would help greatly to reduce our problem. It is up to each individual to police himself for such oversights.

I believe that if we wish to gain public support in our struggle against increasing liability and liability insurance premiums, we will have to demonstrate a willingness to clean up our own act. There is a quid pro quo to gain such support. There must be a demonstration that an improved position in the courtroom will be accompanied by an even higher quality of medical practice than we now give. I have discussed this with politicians and lawyers, and they seem of a mind in this regard.

ArMA is working to develop rapport and common goals with the State Bar Association and other groups. It will require a broad based cooperation to even begin to improve the liability situation, but we cannot, as a single professional group, go it alone to achieve our goals. The fortress mentality will not suffice.

There have been, and will continue to be, frank discussions with MICA about why and whether insurance rates must be as they are. All this will be done in the hope of developing a factual base to convince physicians, lawyers, legislators, and the public that a problem does truly exist and that the very existence of a medical profession in the state of Arizona is gravely threatened.

This is an endeavor which every Arizona physician should support enthusiastically ■

Robert S. Hirsch, M.D.

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Some Things Old Are New Again

The Latest News in Arthritis Therapy

With arthritis striking one in seven people in this country, it is no wonder our patients frequently ask if there is anything new in arthritis treatment. It's a justifiable question. The answer is yes—much is new, although it is often based on something old.

Salicylates Although salicylates have been around more than a hundred years, new studies and endoscopy research suggest that a fresh look be taken at their use to treat arthritis. These studies confirm that nonacetylated salicylates such as salsalate significantly bypass the greatest problem we face in arthritis therapy—nonsteroidal anti-inflammatory drug (NSAID) gastropathy.[1] In addition, salsalate for the first time has been shown to be as effective an anti-inflammatory as aspirin in a mullti-center study.[2]

Two decades ago, it was discovered that aspirin and other NSAIDs blocked prostaglandin synthetase and believed that this explained their anti-inflammatory effect. It is now known that prostaglandins are both pro- and anti-inflammatory. Mounting evidence indicates that blockade of a major cytoprotective and vasodilatory product of prostaglandins, prostaglandin E2 and prostacyclin, accounts for NSAID gastropathy.

The nonacetylated salicylates such as salsalate appear to be cytoprotective while being analgesic and anti-inflammatory.

Sparing NSAIDs More than 100 NSAIDs have been studied for at least the last decade. Carprofen and etodolac are new proprionic acids and nabumetone is a new non-acid pro-drug that all demonstrate prostaglandin and prostacyclin-sparing potential. In the long history of carprofen clinical trial research, only one gastric ulcer has been reported; this from our endoscopy trial. However, that as well as the nabumetone endoscopy research, confirmed lesser gastrotoxicity than commonly used NSAIDs as ibuprofen and naproxen respectfully.[3,4]

NSAIDs are still the backbone of all forms of arthritis therapy and are nearly always used on a long-term basis. Therefore, safety is a vitally important issue.

Methotrexate Available for about 45 years, methotrexate has been stigmatized by concern for liver toxicity, but methotrexate has value in the treatment of rheumatoid arthritis in properly selected patients.

Methotrexate therapy works faster and more consistently than gold or penicillamine therapy, without the degree of toxicity that occurs with some of the disease-modifying antirheumatic drugs (DMARDs).

This is another example of reevaluating an older drug in light of new information and using it in a much safer application.

Stress modification New data show that hope and positive psychological stress-modifying techniques impact on the immune system in an important way for those with chronic diseases such as rheumatoid arthritis.[5]

Clinicians know that depressed, unsupported, acutely or chronically stressed patients with rheumatoid disease get worse. Although it is not known which is cause and which is effect, it is known that encouragement and modification of stress can help to bring about better outcomes.

While research may be decades away from cures, it is still making progress toward better arthritis management.

We can use new technology and information to re-assess available measures and agents and offer our patients safer and more effective arthritis therapy than was possible just a few years ago.

Sanford H. Roth, M.D.

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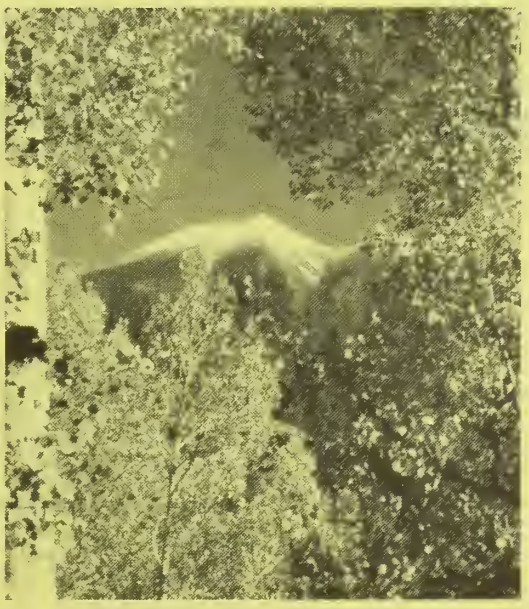

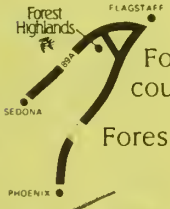

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Aggressive

William B. McGrath, M.D.

The aggressive personality disorder represents the upper side of a coin, opposite to the passive-aggressive. There is nothing subtle or indirect in the aggressive's demand to have his own way, whether it be at the expense of others or not.

Both the aggressive and the passive-aggressive have several basic features in common, and they share them with six or seven other personality disorders. (Inadequate, schizoid, paranoid, cyclothymic, sociopathic, obsessive-compulsive, histrionic) They all have their origin and their arrest in puberty or the latency period. They are very egocentric. They are just beginning to learn that their behavior has consequences, but still only for themselves. So they are not yet considerate of others. And they do stay in character; i.e., their reactions to different situations are usually consistent with their diagnoses.

Aggression may be primary or compensatory. The former is like that of our hypothetical firstborn. From the beginning he had certain advantages over any younger sibling and he could simply take those advantages for granted.

The softer type, compensatory aggression, is manifested by the individual whose masculinity was threatened before it could be firmly established. Such might be the case when a boy has an older sister.

On the one hand the older girl will naturally be dominating. Then too, the lad is forbidden uninhibited awareness of his sister's sexuality or his own. He may henceforth have to keep proving or flaunting his masculinity, staying constantly on guard against symbolic emasculation. This seems unnecessary and rather foolish, of course. Yet the trait may survive inside the closed circle of his egocentricity (the windowless monad of Leibnitz?)

The aggressive, forever childish, has not clearly separated his sex drive from aggression. So romantically he will be a conquistador. Whether invited or not he will make a pass at anything in skirts: included are the wives of his "best friends." He is really making love to himself, using the female as no more than a mirror or foil. When he teases or gets fresh with a saleslady or waitress, there is a barb of cruelty or bullying since any showing of annoyance or disdain on her part will put her job in jeopardy. The aggressive is the sadist, of course, in sado-masochistic transactions.

Under the influence of no more than a couple of drinks or with cabin fever or fatigue, the aggressive suddenly becomes even more offensive, picking quarrels and acting like a child who needs a spanking and is asking for it.

Conversely, when it serves his purpose he can turn on a lot of charm. He seems generous to a fault, but this is deceptive. He will do anything in the world, not toward what *you* want or need, but only if it is what he wants to do, and only when it reinforces his feelings of superiority and dominance.

The aggressive is less disposed to carry a grudge than the passive-aggressive. He is not especially sensitive to real or imaginary criticism, and his self-esteem is lacquered to a high gloss, deflecting insult or rebuke.

There are other differences between the reactions of the aggressive and the passive-aggressive. For a tiny example, suppose there is disagreement over the spelling or punctuation of a word. The passive-aggressive might argue that he is not necessarily wrong. But he will be conciliatory. Not so, the aggressive. He will get out of bed and go all the way to the other end of the house to find a dictionary to prove that he is right. He is not looking for conciliation or compromise; he wants dominance.

A lawyer of our acquaintance is the personification of the aggressive personality. The adversary role fits him like his tailored suit. Even on social occasions he tends to challenge any comments, usu-

ally starting to contradict the speaker before he can have completed a sentence. He has nonnegotiable opinions, even in his companion's field of expertise.

A salesman cannot too easily take "no" for an answer. He has to develop a left jab of assertiveness if he ever hopes to get the attention of the purchasing agent. Executives, too, need a certain toughness to make hard decisions and to terminate unsatisfactory employees. One can sympathize with some minorities: The more aggressively they try to overcome prejudice the more they reinforce it.

Entertainers, especially comedians, are notorious for the vicious means by which they will protect their spotlighted territories. Many comedies feature nothing more than one-liner put-downs of the self-important or the prominent who cannot defend themselves (though this is sometimes passive-aggressive).

The trappings and truncheons of law enforcement and the military attract some aggressives, as they did so many Nazis or fascists. Their officers, however, are more often paranoid.

A playground bully may later find a profitable outlet for his aggression in professional sports like football or hockey. Auctioneers and heavy-jawed, bible thumping preachers seem to thrive on the apparent submissiveness of the folks in attendance.

If the aggressive does have the blessing of primogeniture, he will have more than his share of self-confidence and optimism. Already having won first place (in the family where it counts most), he will always plan to be a winner. He will expect the world to treat him like an heir apparent, as his parents did. He will be uncomfortable with other aggressives, and he will privately look down on those of us who do not enjoy his confidence and forwardness and optimism.

So, it would never occur to the aggressive to pay a compliment or solicit your opinion or ask anyone's permission. In adult life he will still leave his clothes to be picked up by his spouse or the maid. He will surely not let the other party terminate a telephone conversation. He will never express concern about the welfare or progress of your family or your children. He will push ahead in a queue or at a counter. In his automobile he turns into a semi-tumescent organ, honking at more civilized drivers or passing them furiously on the right; protruding halfway into the crosswalk; parking in the fire zone or in a space reserved for the physically handicapped. Enwrapped in the self-centeredness of the latency period (puberty) the aggressive will grieve very little at anyone else's misfortune or death.

Well, there is a pecking order in every hutch and coop and in every real or symbolic human enclosure. This is too bad. One can get along with the aggressive only by recognizing him and knowing what to expect and what not to expect.

In the prevention or redirecting of any of the personality disorders, especially the aggressive, one strategy should be emphasized. Helpfulness and graciousness should be asked of the child. Now a sacrifice is not a sacrifice if it is well-rewarded. When the youngster, on request, shows consideration or generosity, our thanks should be casual, almost perfunctory. This will help teach him that to be considerate of others is natural and should be taken for granted. Such will prove a most encouraging portent of oncoming maturity. ■

William B. McGrath, M.D.

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Arizona Task Force Addresses Liability Crisis

Twenty-two members of a statewide task force appointed to find solutions to the liability crisis facing Arizona's physicians subdivided themselves into nine committees, each charged with researching individual facets of the liability crisis and making recommendations to the group as a whole.

The committee, which met in late July, will meet again in mid-September to hear and react to subcommittee recommendations.

The subcommittee topics and members are:

- Ways to reduce the number and severity of malpractice incidents — Ted Williams, Department of Health Services, Chairman; Joseph Buxer, M.D., gynecologist and former obstetrician; John T. Wrzesinski, M.D., general surgeon and member of the Board of Medical Examiners.

- Workmen's Compensation in Arizona, its ratio of expense to claims paid, how it might be adapted to settling malpractice claims and whether it could handle malpractice fund costs —Jerry LeCompte of the Arizona Workmen's Compensation Claims Fund, Chairman; Neil Barnes, private consultant. Additional subcommittee members appointed were John Rivers, Arizona Hospital Association, and Bob Theilmann, Casa Grande Regional Medical Center, to study the effect of compensation contracts on health care facilities; and Denise Hallfors, R.N., Arizona Nurses Association, and Greg McFarland, Arizona Dental Association, to evaluate the effect of compensation contracts on dental, nurses and other associations.

- Study the State of Virginia's birth-related neurological injury compensation law — Susan Gallinger, Department of Insurance, Chairman; State Representative Jim Meredith, Joseph Hanss, M.D., John Rivers. Additional topics charged to this subcommittee included: reporting the latest studies made by insurance regulatory agencies regarding malpractice statistics, investigating actuarial costs and availability of compensation contracts (Neil Barnes and Fred Cuthberston); and studying the possibility of a pilot project such as that suggested by the Health Policy Agenda for the American People (Diane McCarthy).

- Study the cost impact of practicing defensive medicine to the total cost of health care — representatives from the Arizona Medical Association and the Arizona Hospital Association.

- Study the form content, language and legislation needed to implement a compensation contract — Representative Jim Meredith and Senator Tony West. Additional topics including ways to reduce costs of liability insurance without tort reform and recommendations for effective tort reform in Arizona: Chic Older of ArMA, Joe Abate, John Rivers, Richard M. Gladding, D.O., Jim Roush of the Arizona Trial Lawyers Association.

- Update the study on distribution of proceeds of the malpractice premium dollar — Jack Brooks, M.D., of the Mutual Insurance Company of Arizona and Susan Gallinger.

- Ways to deal with the emergency situation in Pinal County — Bob Theilmann and State Senator Alan J. Stephens.

- Study the stress factor on medical practitioners under the tort liability system — Joe Buxer, M.D., Richard Gladding, D.O., Joe Hanss, M.D., and Brian Finkel, D.O.

- Survey public acceptance of patient compensation — Jim Roush. ■

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If so, please let us know. Call Arizona Medicine at 246-8901 in Phoenix, or 1-800-482-3480 toll-free statewide. We'd love to share the good news with medical professionals throughout Arizona.

Everett W. "Rett" Czerny, M.D., was honored by colleagues at St. Mary's Hospital and Health Center, Tucson, upon his retirement after a 35-year surgical career.

A leading Tucson surgeon, Dr. Czerny served as chairman of surgery and as president of the medical staff at St. Mary's, where he spent almost his entire medical career. A member of the Arizona Chapter of the American College of Surgeons, he served as its secretary-treasurer.

Dr. Czerny served as a delegate from the Pima County Medical Society to the Arizona Medical Association House of Delegates in the mid-60s, and was appointed to the Board of Directors in 1968 as a Southern District Director for a two-year term.

A native of Brooklyn, N.Y., Dr. Czerny earned his undergraduate degree at Dartmouth University and was graduated from the University of Pennsylvania Medical School.

He was licensed to practice medicine in Arizona in 1952 and became board certified in surgery the same year.

His colleagues at St. Mary's commended him for his "immeasurable contributions" to the hospital, its patients and staff, and the Tucson community, which are evidenced "by the respect of his colleagues, hospital and medical office personnel."

The 1987 officers of the Arizona Society of Otolaryngology and Head and Neck Surgery are: President Keith E. McReynolds, M.D., Mesa; President-Elect Dennis Berry, M.D., Phoenix; Secretary-Treasurer Phillip Daspit, M.D., Phoenix.

Vincent A. Fulginiti, M.D.

In spite of a clear understanding of the problem, organized medicine has failed to formulate concrete proposals to remedy the glut of clinical pediatricians and dearth of pediatric scientists produced by America's medical schools, according to the Vice Dean of the University of Arizona's College of Medicine, Vincent A. Fulginiti, M.D. **(Continued on Page 19)**

Family Support Groups for Medical Students

When we asked in mid-1986 whether a parents' group for University of Arizona College of Medicine students should be formed, the typical response went along these lines:

Even though parents' clubs associated with students in undergraduate programs are becoming increasingly popular, the typically more mature, more self-reliant, sometimes married medical student would not want Mom and Dad to be involved—that would be treating the students like children. Our annual Parents Day, held each Fall, does involve a large number of parents, spouses, and "significant others" (SOs), along with the students, in get-acquainted orientation activities, but that is as far as the students want to go.

However, times and attitudes are changing. We found support among many parents, especially two men whose sons had recently graduated from our medical school. One of the fathers was a counselor and the other a financial expert who works with scholarships and financial aid for medical students. These men told us that their sons, and many of their sons' classmates, needed help that could best be provided by a parents' group, and that students would welcome such an initiative. The whole gamut of new issues in medicine and medical education, not to mention the traditional challenges that face medical students, produce high anxiety among some students.

In less than a year from that time, two Family Support Groups for Arizona medical students were formed and operating—one in Tucson and one in Phoenix. Early on a second-year medical student stopped by the office and said: "We (students) think that what you are doing (with the Family Support Groups) is neat." At the same time, he inquired about the Family Support Group service which assists Phoenix clerkship assigned students locate suitable and affordable temporary housing.

The first formal sampling of attitudes toward a parents' group was part of the program for annual Parents Day in October 1986. The concept was described to the audience by the counselor whose son had recently graduated, and simple survey forms were distributed. Responses were highly supportive, and surfaced the idea that the organization should be called "Family" support, not just "Parents...," because spouses and SO's also wanted to be involved.

A steering committee of parents sponsored a poll of the medical students to find what, if anything, students might look to the family group to do. Results: Financial Seminar for Medical Students, yes 50, no 6; Personal Counseling for Medical Students, yes 19, no 12; Career Counseling (by parents who are M.D.s), yes 21, no 8; Housing in Phoenix for Clinical Students, yes 20, no 10; Education for Families about your Medical Education, yes 20, no 4; Stress Management, yes 20, no 9. A variety of other suggestions were given in the free-response section of the survey form. In addition to the survey responses, student-elected class representatives endorsed formation of the family group.

First organizational meetings held in Tucson and Phoenix featured information for family members on the medical curriculum and insight into the experiences of medical education. Any inventory of resources offered by family members was begun, and organizational activities proceeded.

Soon, needs of the family members for better understanding of their students' challenges and stresses in medical school, and for help for the family members in working through their own anxieties as well as assisting their students to do the same, became evident. Programs responding to these needs, featuring senior professionals, have been presented by the Family Support Groups in Tucson and Phoenix.

Receptions sponsored by the Family Support Groups for fami-

(Continued on Page 19)

The Do's and Don'ts of Writing a Personnel Manual

Some physicians and office managers prefer to make policy decisions on the basis of personnel hunches, likes and dislikes, or just plain delight in running the show. They don't want to delegate authority in hiring and firing, or rewarding and punishing employees. But that's a risky and time-consuming way of managing personnel. Eventually every practitioner finds that his life would be a lot easier—and his employees a lot happier—if the policies he/she is constantly being called on to make were written down.

Any practice with more than 15 employees, and even with as few as five, should issue a policy handbook. It should answer some of the most important questions employees ask—questions about salary review, holidays, benefit programs, leaves of absence, and other critical policies that often affect morale and whose absence can create legal problems. The handbook should have two goals: It should keep all employees informed about regulations and changing policies, and it should give supervisors the support they need when they have to enforce those regulations and policies.

The following is an outline of the major items that should be included in a personnel policy handbook, along with some do's and don'ts to consider when you're drafting or revising a handbook.

George S. Conomikes *is president of Conomikes Associates, Inc., practice management consultants, headquartered in Marina del Rey, California with offices in Phoenix, Arizona. The Conomikes organization regularly presents practice management workshops in association with ArMA and other medical societies.*

Physical examinations. Establish your right to conduct both pre- and post-employment physical exams, at the practice's expense. Be sure your decisions to conduct a physical are non-discriminatory—i.e., don't just examine older people or minorities.

Probationary period. Define the period (usually 30, 60 or 90 days) during which a new employee can be dismissed without a hearing on the cause; also indicate when benefits start to accrue. Avoid a great discrepancy between probationary period and the period before an employee qualifies for group insurance.

Hiring of relatives. State whether you will allow a married couple or close relatives to work together. Exceptions might be made for part-time or temporary help.

Work hours. Define the workweek and time allotted for lunch and breaks. Indicate the cut-off time for each pay period. Provide yourself with the option of rescheduling individual hours or work in any given week at the discretion of the supervisor.

Employee status. Define the nature of each type of employee—full-time, part-time, temporary and "non-exempt." Make clear what benefits each is eligible for. Be specific to avoid any chance of misunderstanding.

Overtime pay. Establish clearly that overtime is paid for work over 40 hours a week, and how much is paid for work on a holiday. Make it clear that pay for overtime must be approved by a supervisor. Don't say that you are bound to assign overtime on the basis of seniority.

Pay reduction for lateness. The usual policy is to go by the clock, i.e., to dock an employee's pay in units of six minutes or tenths of an hour. Using too large a unit, such as a quarter of an hour, may cause problems. It may be illegal to dock an employee's pay by that much if he is only a few minutes late.

Severance pay. Have no policy.

Performance review and merit increases. Review wages either on the anniversary of employment or during a set annual period. This policy is essential—some employees would rather quit than ask for a raise. Don't commit yourself to cost-of-living increases; make all raises based on merit.

Time clock or sign-in system. Rules should prohibit employees from recording another's time, causing another employee to record for him, or failing to record his time. Rules also should forbid signing in too soon or out too late without authorization. You must keep some sort of record of hours worked by "non-exempt" employees. Early sign-ins or late sign-outs will make you liable for overtime pay in case of a conflict or dispute.

Emergency shutdowns. Consider whether you will pay some minimum "call-in" wage in case you have to close down because of bad weather, a power failure, or some other unforseen problem. What advance notice will you provide, if possible, in the event of such a shutdown? Make sure you treat everyone the same. If you pay the regular wage to those who don't show up, you should pay those who do come in something extra.

(Continued next page)

Group insurance benefits. State coverage generally and briefly, indicating what portion of premium costs the company pays for, how long a new employee has to wait for coverage, etc.

Holidays. List all holidays, and state how long an employee has to work to qualify for a paid holiday. Also indicate that employees have the right to take religious holidays without pay. What happens if the holiday occurs during an employee's vacation? What pay is given for work on a holiday? Leave some room to reschedule a holiday depending on business conditions. You don't have to pay overtime in a week with a holiday unless more than 40 hours are worked.

Vacations. Most practices provide two weeks paid vacation annually. Probably half increase this to three weeks after 5-7 years of employment. And some offer four weeks after 10-15 years on the job. Vacations should not be awarded until an employee has been on the job for at least six months, preferably twelve months. May a person choose to work instead of taking a vacation? May one take off more than two weeks at a time or as little as a day at a time? Are permanent part-timers given any vacation? Will accrued vacation pay be given at severance? Will a person on leave of absence accrue vacation time? Don't let vacation scheduling supersede the needs of any individual department. Check state laws regarding payment of accrued vacation time at severance.

Personal time/sick leave. Six to 10 days per year is the typical number of sick days allowed. Give employees the option of accumulating a reasonable number of days (20 or 30) for the future, or create a payback system for those who don't abuse the privilege. The advantage of calling it "personal time" rather than "sick leave" is that employees will take sick leave without giving advance notice. Require "proof of illness" if you pay for time off only in the case of illness. Don't let personal time accrue during an extended leave of absence.

Disability leave of absence. Federal law requires leave time for disability due to pregnancy to be equal to that allowed for disabilities that affect only males. You must set some reasonable time limit during which you will guarantee job protection for a disabled worker. A 60-to 90-day period is typical. You may require pregnant women to sign statements of intent to return to work provided you require male workers disabled for other reasons to do the same. You may also reserve the right to require a physical examination by a practice-appointed doctor if required of both males and females. You do not have to have a leave policy at all if you don't want it, but some states have laws requiring a minimum leave time for pregnant women.

Personal leave of absence. If you decide to grant such leaves, you may want to specify that they may not exceed 30 (or 60) days, and that they may not be taken to look for or perform another job, or to start another business. You may want to omit this item and play it by ear. If you plan to grant only discretionary leaves, omit this item.

Don't require the employees sign over to the company the checks they receive from serving on a jury. This may cause tax problems.

Jury duty. You must allow employees time off for jury duty (and you must continue their employment after they return from jury duty). However, in most states, you don't have to pay employees for their jury duty service — and most employers don't. Depending on local laws, you may want to set limits on how many days of jury duty you will pay for, and set a qualifying period of employment before you will pay for jury leave. Don't require that employees sign over to the company the checks they receive from the court for serving on a jury. This may cause tax problems. Just pay them the difference between the amount of the check and the pay they would have received.

Bereavement pay. Employees expect the company to be very lenient in this matter. Typical policy allows three to five work days off with pay in the event of a death in the immediate family. Absence of a policy of some sort is bad for morale, but it's important to be consistent in granting the benefit.

Pension or profit-sharing plan. Mention that you have a plan, when and how the employee becomes qualified for it, whether an employee contribution is permitted or required, and when an employee becomes vested. Don't go into great detail; refer instead to a separate description of the plan.

A lawyer is the best person to consult before you issue a policy statement to employees. (Remember, a policy handbook may be considered legally binding in the event of a dispute or an unfair employment practice claim.) ■

George S. Conomikes

New Active Members

The Arizona Medical Association welcomes the following new members:

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Jonathan A. Agbebiyi, M.D.
Obstetrics & Gynecology
4614 E. Shea Boulevard
Suite D-110, Phoenix
University of Michigan
Medical School - 1978

Lucio Arteaga, Jr., M.D.
Family Practice
3301 North Miller Road
Suite 160, Tempe
Fac. Med. Univ. Autonoma
de Guadalajara - 1979

Quinton C. Callies, M.D.
Internal Medicine, Allergy & Immunology
13400 East Shea Boulevard, Scottsdale
University of Wisconsin
Medical School - Madison - 1960

Melvyn A. Chase, M.D.
Dermatology
2525 West Greenway Road, Phoenix
Wayne State University
School of Medicine-Detroit - 1968

Ernest Feigenbaum, M.D.
Public Health
1845 East Roosevelt Street
Phoenix
New York Medical College - 1960

Douglas D. Frye, M.D.
General Practice
2740 South Alma School Road
Suite 1, Mesa
University of Colorado School
of Medicine - 1982

Keith D. Goldblum, M.D.
Emergency Medicine
1947 East Thomas Road, Phoenix
University of Missouri-Kansas
City School of Medicine - 1978

Gabriel P.N. Lombard, M.D.
General Practice, Administrative Medicine
1600 West Broadway
Suite 245, Tempe
University of California Irvine
College of Medicine - 1967

Paul R. Love, M.D.
Dermatology
1520 South Dobson Road
Suite 320, Mesa
University of Michigan
Medical School - 1983

John C. Maisel, M.D.
Pathology
1916 West Bethany Home Road
Suite 120, Phoenix
Albany Medical College
Union University - 1957

William R. Marsh, M.D.
Pediatric Allergy, Allergy & Immunology, Pulmonary Diseases
5310 West Thunderbird Road
Suite 215, Glendale
University of Texas Medical
School-San Antonio - 1979

Marlin D. Mills, M.D.
Obstetrics & Gynecology, Maternal/Fetal Medicine
Fac de Madicina de Universida
de Guadalajara - 1878

Craig B. Reeder, M.D.
Hematology, Internal Medicine
13400 East Shea Boulevard
Scottsdale
Southern Illinois University
School of Medicine - 1978

Marc R. Sanders, M.D.
Anesthesiology
3150 North 24th Street
Suite 103, Phoenix
Fac Med Universida Autonoma
De Guadalajara - 1975

David R. Sanderson, M.D.
Internal Medicine, Pulmonary Diseases
13400 East Shea Boulevard
Scottsdale
Northwestern University
Medical School - 1958

Ngampen B. Savetamal, M.D.
Pediatrics, Family Practice
8155 West Thunderbird Road
Peoria
Fac of Med at Siriraj
Hospital University - 1961

Robert M. Siegel, M.D.
Cardiovascular Diseases, Internal Medicine
145 Centennial Way, Mesa
Fac of Medicine & Surgery
University of Roma - 1977

Richard E. Sledden, M.D.
Family Practice, Geriatrics
10240 West Bell Road
Sun City
Yale University School
of Medicine - 1958

Kurt E. Springmann, M.D.
Anesthesiology
8714 East San Miguel, Scottsdale
University of Arizona
College of Medicine - 1984

John C. Timmes, M.D.
Obstetrics & Gynecology
1901 East Thomas Road
Suite 207, Phoenix
Medical College of
Pennsylvania - 1976

Nina W. Wilkey, M.D.
Obstetrics & Gynecology
5310 West Thunderbird Road
Suite 308, Glendale
University of Arizona
College of Medicine - 1981

Robert O. Wilson, M.D.
Orthopedic Surgery
12238 North 113th Avenue
Youngtown
University of Utah
College of Medicine - 1969

MOHAVE

Thomas G. Dallman, M.D.
Internal Medicine
2724 Silver Creed Road
Bull Head City
Medical College of Wisconsin-
Milwaukee - 1983

Craig D. Diehl, M.D.
Pediatrics
1951 Mesquite Avenue
Lake Havasu City
American University of the
Caribbean - 1983

William L. Shankel, M.D.
General Surgery
1060 Highway 95, Bull Head City
University of Connecticut
School of Medicine - 1979

PIMA

Kenneth W. Blecher, M.D.
Orthopedic Surgery
630 North Alvernon Way
Tucson
University of Illinois
College of Medicine - 1964

YAVAPAI

Clifford M. Morgan, M.D.
General Surgery
P.O. Box 1535, Cottonwood
University of Arizona
College of Medicine - 1979

YUMA

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Anesthesiology
1405 West 16th Street, Yuma
University of Illinois
College of Medicine - 1980

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Internal Medicine
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Tuba City
Yale University School of
Medicine - 1975

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School - 1946

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Obstetrics & Gynecology
10420 Pineaire Drive, Sun City
University of Pennsylvania
School of Medicine - 1950

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Family Practice
Phoenix Baptist Hospital
University of Arizona
College of Medicine - 1984

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Anesthesiology
Maricopa Medical Center
Fac of Medicine University
Autonoma De Guadalajara - 1979

William J. Rice, M.D.
Anesthesiology
Maricopa Medical Center
University of Texas Medical
School - San Antonio - 1984

Charles M. Smith, M.D.
Internal Medicine
Maricopa Medical Center
University of Oklahoma
College of Medicine - 1984

To The Editor:

Peer review, the darling of the Joint Commission and Medicare bureaucrats, has become an integral part of hospital politics and management and may, if properly utilized, serve as a useful tool while assessing quality control. Although, most of us have significant distaste for the task, it behooves us to be alert to the ramifications of it. This cannot be performed by a computer or someone who thinks like a computer but can only be performed by individuals trained in the area of question.

To guard against the problem of the over zealous reviewer, I would suggest that we change our approach from the time honored volunteer program to that of a universal draft.

To ensure that there is no favortism, each active member of the medical staff will serve a specified time on the utilization committee. The term in office should not exceed one month; and if the staff is large enough, two weeks would be more appropriate. If we accept this, we will provide the entire staff with whatever educational benefits are to be derived from serving on the utilization committee; bring timid members of the staff into the mainstream of the hospital political process; and, finally, disengage territorial philosophies.

Howard H. Johnston, M.D.

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Family Support Groups

(Continued from page 12)

lies of new students for the 1987-88 academic year are expected to bring additional parents, spouses, and SO's into structure. We believe that this will lead to continued benefits to family members as well as students, and ultimately, the college and university through greater involvement of these people.

Richard G. Frohnen, Ed.D.
Director
Development Office
Louis J. Kettel, M.D.
Dean
College of Medicine
University of Arizona

Vincent A. Fulginiti, M.D.

(Continued from page 11)

Nor, he charged, has organized medicine devised specific strategies or tactics to reach any of what should be the nation's pediatric goals.

In an editorial recently published in the *Journal of the American Medical Association (JAMA)*, Dr. Fulginiti critiqued a recent study by the AMA Council on Long Range Planning and Development, which was produced in cooperation with the American Academy of Pediatrics.

"The report is admirable in its description of the problem; it is short on dealing effectively with it," Dr. Fulginiti wrote. "As one surveys (its) recommendations, one is impressed with their nonspecificity, their global nature and relative impotence.

The recommendations, he wrote, do not lay out either strategy or tactics to reach our goals, which should include:

- Reducing poverty;
- Assuring access to medical care for poor children;
- Adjusting the number of clinical pediatricians who will enter the profession by reducing or adjusting the number of pediatric residencies;
- Redistributing the excess number of pediatricians to underserved areas; and
- Encouraging the education of young, talented pediatrician-scientists to replace the aging specialists who now populate the academic ranks.

Organized medicine, he wrote, must insist on specific action by working through Congress and the administrations of the nation's medical schools and hospitals to address the problem.

Changes in physician reimbursement plans are also long overdue, Dr. Fulginiti wrote. "We have tolerated for too long, with much too passive an approach, the disproportionate payment for catastrophic care and for procedure-oriented activitiy.

"Our agenda for seeking adequate compensation should have as its first priority the placing of cognitive care at a higher level, balanced by a reduction in the compensation for non-cognitive care, to keep the total cost within bounds."

Dr. Fulginiti encouraged support of the Child Health Incentive Reform Plan, which demands that well-child care be included in employer-based health care plans. The American Academy of Pediatrics is the major advocate of this program.

The council report shows that the number of pediatricians practicing in the United States grew by 89.3 percent from 1970 to 1985, in contrast to a 21 percent growth rate in the population of children younger than 10 years of age. The number of all physicians grew by only 65.5 percent during this period. In addition, the number of women entering pediatrics has increased faster than the number of women entering medicine overall, and graduates of foreign medical schools also make up a large and growing share of pediatricians.

Increase In Cases Of Gonorrhea Resistant To Penicillin

An increase in cases of gonorrhea resistant to penicillin has been noted in the Phoenix area, according to the Maricopa County Health Department. Usually only about two percent of cases are resistant to penicillin, the antibiotic most frequently used to cure the infection. The increase was first noted in June when about 5 percent of cultures from the Maricopa County Sexually Transmitted Disease (STD) Clinic were resistant. In July the percentage of resistance has climbed to over 10 percent. Cases have occurred throughout the valley among heterosexual men and women ranging in age from 16 to 45.

Because of the increase in antibiotic resistant cases, the STD Clinic has instituted the use of ceftriaxone, and antibiotic given by injection, for all cases and contacts to gonorrhea. Futhermore, specific treatment and control guidelines are being mailed to all physicians in the valley indicating the recommended antibiotic changes.

Physicians are being encouraged to report resistant cases by phone to the STD clinic so disease investigators can locate and treat potentially infected contacts. Since few laboratories test gonorrhea for drug sensitivities they

are being encouraged to send gonorrhea cultures to the county STD laboratory for this type of testing.

Resistance to penicillin can occur in two ways. The bacteria can produce an enzyme that destroys penicillin (Penicillinase producing *Neisseria gonorrhea* (PPNG) or the organism's genetic structure can produce the drug resistance directly (chromosomally mediated resistant *Neisseria gonorrhea* (CMRNG). PPNG has been a recurrent threat in the U.S. since the 1970's, while CMRNG has more recently emerged. Chromosomal changes can also cause resistance to other antibiotics such as tetracycline. There is preliminary evidence that some cases in Maricopa County are tetracycline and penicillin resistant.

This outbreak is the first evidence of widespread CMRNG activity in the state. Intensified monitoring and special treatment and control measures are expected to be necessary for the next two to three months.

For further information, contact: S. J. Englender, M.D., M.P.H., 230-5808, Harvel Alishouse, D.V.M., 230-5816, Arizona Department of Health Services; or Charles Juels, M.D., Maricopa County Health Department, 258-6381. ■

Rare, Dangerous Effect of Anorexia Nervosa

A report in July's *Archives of Surgery* describes a rare, severe complication of anorexia nervosa and bulimia, the starvation/binge-purge behaviors often seen in young women obsessed with thinness. Rashid A. Abdu, M.D., and colleagues at St. Elizabeth Hospital Medical Center, Youngstown, Ohio, report cases of gastric infarction, or stomach rupture, in two teenage girls. The authors found only three other cases in the literature; of the five, young women aged 14 to 22 years, only three survived. Surgical treatment was delayed in all five because the diagnosis was missed initially or the patient did not seek treatment. It appears starvation or anorexia can cause loss of muscle tone and atrophy in the stomach; sudden food ingestion can then cause paralysis, leading to acute gastric dilation. If this continues, severe damage can result. "Physicians should be alerted to the possibility of acute gastric dilation if a young woman, who may be undernourished and anorexic, complains of abdominal pain after ingestion of a large meal," the study says.

Predicting Relapse in Schizophrenia

While drugs can be used to treat many schizophrenics, clinicians don't have a good way to predict the course of the illness or identify patients who could remain stable on lower drug doses. A report in July's *Archives of General Psychiatry* now suggests such a test may be possible. Jeffrey A. Lieberman, M.D., of Long Island Jewish Medical Center, Glen Oaks, New York, and colleagues studied 34 stable schizophrenics on drug therapy who were given a "challenge" test with methylphenidate, a drug that selectively inhibits neuronal uptake of the neurotransmitter dopamine, high levels of which have been implicated in shcizophrenia. Specific measures of behavioral, cardiovascular and neurologic response to the test were associated with time and tendency to relapse after withdrawal of drug therapy, the study says. "These measures may be potentially useful in the identification of candidates for (drug) withdrawal and/or dosage reduction treatment strategies," it concludes.

Anti-Drug Videotape Available Through ArMA

Physicians who work with addicted teenagers are encouraged to contact Arizona Medical Association headquarters to schedule a preview of a new videotape told in the words of recovering teen addicts.

The 15-minute tape, produced under the supervision of the Oregon Medical Association, is designed to clearly communicate to teenagers the dangers of drug abuse. It is to the producer's credit that the tape succeeds without "preaching."

Produced in a modified MTV style selected to appeal to young audiences without offending parents, the message is aimed directly at those confronting drug and alcohol abuse. Its producers hope physicians and counselors across the country will make the tape available for viewing by teens with substance abuse problems.

Physicians interested in previewing the tape should call ArMA's communications director, Susan Fuchs, to schedule a time to see the videotape. The original tape cost ArMA $88, but its producers have said that if ArMA orders copies in bulk, there will be a discount. ■

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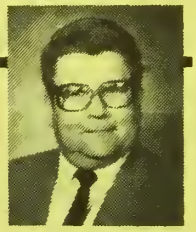

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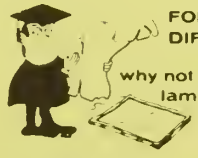

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Electrolyte, Blood Urea Nitrogen and Glucose Level Screening in Medical Admissions

Impact on Patient Management

LLOYD RUCKER, MD; F. ALLAN HUBBELL, MD, MSPH; BARBARA V. AKIN, MD, *and* ELIZABETH FRYE, MD, *Orange, California*

Investigators have failed to show the usefulness of screening electrolyte—sodium, potassium, chloride and bicarbonate—blood urea nitrogen and glucose levels. In spite of this, we observed that that practice continues to be widely used at our university medical center. Using a form of consensus analysis, we examined the records of 301 admissions to the medicine service to determine whether laboratory tests were done for diagnostic or screening purposes and whether screening test results led to changes in patient management. Of the 1,764 tests done, 716 (40.6%) were for screening purposes. Only 2 (0.3%) screening test abnormalities led to any therapeutic changes, and many false-positive tests led to unnecessary diagnostic retesting.

(Rucker L, Hubbell FA, Akin BV, et al: Electrolyte, blood urea nitrogen and glucose level screening in medical admissions—Impact on patient management. West J Med 1987 Sep; 147:287-291)

In the early 1960s, automated processes became available for measuring serum chemistries. These processes were perceived as valuable because a wide variety of tests could be done relatively inexpensively using a minimal amount of blood. As a result, many clinicians began to advocate the use of these panels for screening purposes.[1,2] Bryan and coworkers, in fact, thought that the exhaustive search for physical findings and history ought to be paralleled by an equally exhaustive "profile admission chemistry."[3] The use of automated panels for screening became widespread. In the intervening years, however, uniformity of opinion concerning the value of routine screening chemistries has not been achieved.[4-7] The disagreement centers not so much on whether abnormalities will be found but on whether these findings will add new, clinically meaningful data to what is already known about a patient. Thus, in the 1980s physicians continue to order serum electrolyte (sodium, potassium, chloride and bicarbonate), blood urea nitrogen (BUN) and glucose tests with the hope that their patients will benefit from the results.

We undertook this study with three specific objectives: to determine the percentage of patients admitted to the medicine service who were screened for abnormalities in the individual component tests, the diagnostic yield of individual tests and whether the results of screening tests changed patient management.

Methods

The University of California Irvine Medical Center (UCIMC) is a 500-bed tertiary care hospital that serves as the primary teaching facility of the California College of Medicine of the University of California, Irvine. The hospital serves a mixed population that is about 70% indigent and about 30% Spanish speaking. An extensive effort was made to retrieve the charts of all patients admitted to the medicine service during the month of January 1985.

Although we have no institutional or departmental policy regarding the tests to be done on admission to the medicine service, our impression had been that serum electrolyte, BUN and glucose levels were determined on most medical admissions whether or not there were specific indications. These tests can be ordered together as a six-factor multiple-analysis panel. It is less expensive to order the panel than to order individually two or more of the tests on it. We used the nominal group process,[8] a form of consensus analysis, to determine which tests were for screening purposes and which screening tests led to alterations in management. Three faculty members of the Division of General Internal Medicine independently examined the medical records of each patient to determine whether any of the tests in question were done. If a test was done, the record was then evaluated to determine whether a specific indication existed for doing the test or whether it was done purely for screening purposes. We defined "screening" as doing any of these tests on a patient in whom a new abnormality or worsening of a previously known abnormality would not have been suspected from the history or findings of a physical examination. To evaluate this question, specific criteria were developed for each test and the chart was reviewed thoroughly for each of these criteria (see Table 1). For instance, if a patient had a history of polyuria, polyphagia, polydipsia, diuretic or steroid use, chronic pancreatitis or diabetes mellitus, hyperglycemia might have been suspected and the blood glucose determination considered "diagnostic." But if none of these factors were present and a blood glucose level was measured, the examination was considered a "screening" test. Indications for the test were kept

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
UCIMC = University of California Irvine Medical Center

narrow and specific. Each of the records was evaluated by using a standard form that contained the indications and criteria. The criteria were agreed on by faculty members of the Division of General Internal Medicine using a consensus approach. Only data available in admission notes were used. Discharge diagnoses were not used to differentiate screening from diagnostic tests since diagnoses may have been generated from results of the screening tests.

After the record was reviewed to determine whether the test was diagnostic or screening, the results of the test were recorded. A judgment was made as to their normality using the standard reference ranges defined by our laboratory. We recognized that for all tests a certain number of "normals" would fall outside the laboratory's specified indices. But we wanted to evaluate the test results as to the manner in which physicians reacted to those results using the defined indices for normal.

After reviewing progress notes and order sheets, another judgment was made as to whether the results led to changes in patient care. Patient care was changed if results appeared to have led to an alteration in either the diagnostic or the therapeutic plan. Each record was reviewed in the same manner to determine if indeed these criteria were fulfilled. In the case of disagreement about the reason a test was done or about a change in patient care, the case was discussed until consensus was reached.

Results

During the month of January 1985, 304 patients were admitted to the medicine service of UCIMC. Of these, the charts of 301 (99%) were available for review. This sample represents about 10% of all medicine service admissions for the year. Consensus was achieved in each case. The results of the review are presented in Table 2. A total of 1,764 individual tests was ordered. All of the tests were done on the six-factor multiple-analyses panel. None were ordered individually. The panel was used for 294 (98%) of the patients. In all, 61 (21%) of the panels were considered to be entirely ordered for screening, and 79 (27%) were either all screening or contained only one diagnostic element. Overall, 716 (40.6%) individual tests were considered to have been done for screening purposes. Of these, 27 (4%) led to a change in test ordering and 2 (0.3%) led to a change in treatment.

The one patient with an abnormal serum sodium level was found to have a value 1 mEq per liter below the lower limit of normal. No action was taken in this case. The low sodium level was not noted as a problem on this admission and had no effect on the patient's course.

Two abnormal serum potassium levels were found. The first was a slightly elevated value noted on a specimen described as hemolyzed. A repeat potassium level without therapy was in the middle of the normal range. The second potassium level was 1 mEq per liter below the accepted range. The patient was a 55-year-old man admitted for chemotherapy for a lymphoma. Treatment consisting of 60 mEq of oral potassium replacement was initiated. Review of the old record showed that although this abnormality had been present in the past, it was not noted in the admission under consideration and was therefore considered a significant screening finding.

Of the seven abnormal chloride levels, all were elevated. Two were repeated and found to be normal. Of the rest, all were within 3 mEq per liter of normal and no chloride level was noted in any record as abnormal or had any meaningful effect on the course of the patient's care. The results did not lead to any change in patient management.

Abnormal bicarbonate levels were found in five of the screened patients. The one elevated bicarbonate level was 1 mEq per liter above normal and was not noted as a problem. Of the four low bicarbonate levels discovered, all were within 2 mEq per liter of normal; two were repeated without therapy and found to be normal, and two were not repeated. In no case was patient care judged to have been altered by an abnormal bicarbonate level.

TABLE 1.—*Criteria for Labeling a Test Diagnostic by History, Signs or Symptoms*

Sodium Level	
Vomiting	Congestive heart failure
Diarrhea	Cirrhosis
Excessive sweating	Hypotension
Excessive fluid intake	Hypertension
Excessive thirst	Dehydration
Polyuria	History of diabetes mellitus or diabetes insipidus
Pulmonary disease	History of renal disease
Central nervous system disease	Drugs known to affect sodium level
Potassium Level	
Vomiting	Renal failure
Diarrhea	Muscle weakness
Glucocorticoid excess	Tissue damage
Glucocorticoid deficiency	Hypertension
Digitalis	Diabetes mellitus
Congestive heart failure	Drugs known to affect potassium
Chloride Level	
Vomiting	Suspicion of acidosis
Diarrhea	Suspicion of alkalosis
Mineralocorticoid excess	
Bicarbonate Level	
Vomiting	Drugs causing acidosis
Diarrhea	Acidifying salts
Small bowel drainage	Respiratory disease
Ureterosigmoidostomy	Muscular weakness
Hyperparathyroidism	Congestive heart failure
Suspicion of acidosis	Renal insufficiency
Diuretics	Mineralocorticoid excess
Hyperalimentation	Dehydration
Glucose Level	
Polyuria, polydipsia, polyphagia	Hypoglycemia agents
History of diabetes mellitus	Altered mental state
Chronic pancreatitis	Sweating
Hemochromatosis	Tremor
Glucocorticoids	Anxiety
Pheochromocytoma	Weakness
Cystic fibrosis	Alcohol abuse
Diuretics	
Blood Urea Nitrogen Level	
Urinary tract infection	Sepsis
Altered mental state	Dehydration
Systemic disease associated with renal complications	Congestive heart failure
	Cirrhosis
History of renal disease	Enlarged kidneys
Drugs associated with renal toxicity	Pelvic mass
	Enlarged prostate

TABLE 2.—*Impact of Screening Electrolyte, Blood Urea Nitrogen and Glucose Levels*

Test Done	Total Tests, No.	No. Considered Screening (%)*	No. Abnormal Screening Tests (%)*	Repeat or Additional Tests (%)*	Change in Therapy (%)*
Sodium	294	101 (34.3)	1 (1.0)	0	0
Potassium	294	90 (30.6)	2 (2.2)	2 (2.2)	1 (1.1)
Chloride	294	163 (55.4)	7 (4.3)	0	0
Bicarbonate	294	115 (39.1)	5 (4.3)	2 (1.7)	0
Blood urea nitrogen	294	121 (41.2)	3 (2.5)	0	0
Glucose	294	126 (42.9)	44 (34.9)	23 (18.3)	1 (0.8)
Total	1,764	716 (40.6)	62 (8.7)	27 (3.8)	2 (0.3)

*Numbers in parentheses represent percent of total.

Of the three abnormal BUN levels, one was slightly elevated and two were slightly low. None of these were noted as a problem and none led to any change in management.

The results of the glucose determinations are given in Table 3. Out of 126 screening glucose levels, 44 (35%) were found to be elevated above the normal fasting range. In all, 23 (18%) led to further diagnostic testing and 1 (0.8%) led to a change in therapy. All but one of the specimens for the initial glucose levels were randomly drawn. Of the 23 fasting blood glucose levels done in response to abnormal screening results, only 1 was found to be persistently elevated. The patient was a 60-year-old woman with newly diagnosed gastric carcinoma who was admitted with gastric outlet obstruction. Her admission glucose level in a randomly drawn specimen was 199 mg per dl. A fasting glucose level was never done, but insulin therapy was started concurrently with hyperalimentation that included a solution of 50% dextrose in water. Although it was not clear that the initial screening glucose abnormality contributed to the decision to begin insulin therapy, we included this patient because we could not exclude the possibility.

Of the abnormal glucose values that were not repeated, none were above 200 mg per dl and 18 were below 140 mg per dl, the level below which even a fasting glucose would probably not elicit a therapeutic response.

Discussion

Expensive technologies are often blamed for the rapid inflation of medical care costs. This must in part be the case. Moloney and Rogers have argued, however, that the increased use of a large number of low-cost procedures also adds greatly to this inflation.[9] In this era of limited medical resources, we must ask whether the continued use of a large number of screening tests has been justified by studies that show that these tests contribute in any meaningful way to the management or well-being of patients. Specifically, in the case of determining electrolyte, bicarbonate, BUN and glucose levels, should screening tests be used to search for clinically important abnormalities in patients without specific indications for ordering these tests?

The results of our study are interesting in several respects. First, it is curious that every one of the electrolyte, glucose and BUN levels was ordered on the panel test. This suggests that a significant proportion of the tests may have been ordered without thought for their usefulness. Overall, 40.6% of the tests was purely for screening as defined by our criteria. Most of the screening tests were probably done not for the specific purpose of screening but because they appear on the same panel as a test that was done for another indication. On the other hand, 21% of the panel tests were entirely for screening (none of the six tests on the panel were for diagnostic purposes). Another 6% of the panels contained only one diagnostic examination and, therefore, the panel could not be justified as cost-saving over ordering individual tests. This suggests that, conservatively, about a quarter of the admission laboratory tests evaluated by us were either for the conscious purpose of screening or were ordered reflexively just because a patient was admitted to the hospital. Even though the most recent literature does not support the use of these tests as admission screening tests, this practice apparently continues in our university teaching hospital (a highly cost-conscious institution due to budget constraints). It probably continues in various forms in other institutions as well.

Out of 590 screening electrolyte and BUN test results, only 4 led to diagnostic responses, and only 1 low potassium level proved to have any therapeutic importance. Indeed, it could be argued that even the one case of hypokalemia could have been predicted from a review of the old record.

Of the 44 patients initially found to be hyperglycemic on random admission screening, only 1 (0.8%) was considered to have true hyperglycemia and therefore received therapy. Of the others, 22 (50%) were found to have misleading screening data and the rest for the most part had such minimally elevated glucose levels that it is unlikely that these asymptomatic patients would have proved to have diabetes mellitus. The one patient who was treated was asymptomatic, never had a fasting glucose level and would have required insulin during hyperalimentation in any case.

Our study included important features not present in previous investigations of screening admission testing. We used a form of consensus analysis to determine which tests were ordered for screening purposes and which led to management changes. Most previous studies relied on observations by single observers. While the consensus analysis approach is time-consuming, the conclusions reached are more likely to be generalizable to other settings and less likely to include systematic biases. On the other hand, because of the extensive effort involved in the consensus process, our study included a relatively small sample size. The design was biased against our conclusion, however, since changes in management could possibly have been introduced for reasons other than the results of screening. In addition, contributory elements of the history or physical examination may have been omitted from the recorded data but used in making management decisions.

As Griner and Glaser have pointed out, the electrolyte panel was designed to assist in management, not as a screening test.[7] An actual screening test must be designed with several criteria in mind: It must be relatively sensitive and specific; it must screen for a disease whose prevalence is

high enough to justify screening; it must screen for a disease that is frequently asymptomatic, and it must screen for a disease for which a therapy exists, and for which therapy at an earlier, asymptomatic stage makes an outcome difference over waiting until the disease becomes symptomatic. Even though it is frequently used for screening, the electrolyte panel was not designed with these criteria in mind.

That theoretical criticism aside, we have found little evidence either in our study or in the literature that screening for abnormalities in electrolyte, BUN or glucose levels provides clinically meaningful information. Table 4 summarizes previous studies using our criteria for meaningful data. A number of authors have failed to document the usefulness or to recommend the use of screening laboratory tests.[7,14,18-22]

When investigators examine the usefulness of routine screening laboratory tests, they often evaluate large panels of tests but not individual elements of the panels. Furthermore, they rarely discuss the criteria for medical importance or the usefulness of the findings. In 1965 Bryan and associates reported a study conducted at the Duke University Medical Center (Durham, NC), a veterans hospital and a local community hospital.[3] In that study, the results of a screening panel done on 2,846 admissions were compared with those of a set of values on specimens drawn only on the day of admission at the discretion of the attending physicians or house staff. About one in ten of the patients had an abnormality discovered that was considered important but that would have been missed without the screening. In a subpopulation at the Veterans Administration hospital, all 623 admissions were evaluated for clinically important abnormalities. Although testing uncovered 22 abnormal values (16 glucose, 1 bicarbonate, 1 potassium and 4 BUN), no mention was made of whether the test results affected management in any way. Furthermore, no attempt was described to determine whether or not the abnormalities could have been predicted from clinical data and were therefore not truly screening tests.

Bates and Yellin conducted a study of the usefulness of multiphasic "screening" of outpatients.[11] Their study design did not meet our criteria for screening. They concluded that physician indifference to results, high false-positive rates and a lack of follow-up crippled any screening effort. Indeed, one of the lessons of our study and others is that abnormal results frequently are not noted or acted on by physicians.[14,23,24]

Studies examining the usefulness of electrolyte screening rarely if ever show that screening adds any meaningful information to the management of a patient.[3,10-12,14,15] With the exception of our one mildly hypokalemic patient, screening has virtually never been shown to conclusively lead to a change in management.

Studies examining the usefulness of screening for hyperglycemia have shown somewhat more equivocal results.[3,10,11,14,16,17,25] Because these studies have been conducted in a variety of settings using various analytic methods, it is difficult to compare them directly. In general, they have shown that even under the most careful clinical scrutiny, occasionally a patient will be discovered to have hyperglycemia that would not have been found without screening. Whether this discovery leads to a meaningful change in therapy is not addressed in most of the studies. Where this issue is addressed, the discovery of hyperglycemia does not seem to make much of a difference in ultimate outcome.[12,14,17]

Authors have argued that screening is useful for reasons beyond the pure and simple discovery of new disease—for instance, the usefulness of being able to reassure a "worried-well" patient that he or she is not ill.[24] This does not apply to a patient admitted to hospital with an acute medical illness and therefore could not be applied to the patients in our study.

Although we did not evaluate this element, we wonder whether the practice of screening patients admitted to a medical service might even erode the process of medical evaluation. By depending on screening rather than thinking, physicians might actually lose some of the diagnostic acumen needed to sort out complex problems.

Although no basis exists for such a practice, physicians at our institution continue to order screening admission electrolyte, BUN and glucose levels. Our data do not support this practice. Indeed, our results suggest that screening may possibly do more harm than good because falsely abnormal results may lead to unnecessary patient or physician anxiety and may also generate needless follow-up laboratory tests. Despite some previous studies suggesting that the use of these tests is not productive, our study shows that the practice continues in at least one university hospital. Misconceptions about the value of these tests for screening remain widespread. We urge individual practitioners and institutions to reexamine their policies in this regard. In addition, we urge that medical educators emphasize decision-making processes for the more rational use of electrolyte, BUN and glucose level testing. Decision analysis methods are being developed

TABLE 3.—*Range of Initial Abnormal Glucose Levels and Repeat Values*

Serum Glucose Level, mg/dl	*Initial Fasting Specimens, n = 1*	*Initial Random Specimens, n = 43*	*Repeat Specimens, n = 23*	*Initial Value of Specimens not Repeated, n = 21*
<115	..	..	22	..
115 to 140	1	29	1	18
141 to 200	0	13	0	3
>200	0	1	0	0

TABLE 4.—*Studies Addressing the Usefulness of Screening Electrolyte or Glucose Levels*

Reference	*Screening (by our criteria)**	*Abnormal Results, %*	*Laboratory Change, %*	*Treatment Changes, %*
Electrolytes				
Bryan et al, 1966[3]	NP	0.3	NN	NN
Belliveau et al, 1970[10]	NP	0	NN	NN
Bates and Yellin, 1972[11]	No	NA	NA	NA
Korvin et al, 1975[12]	Yes	1.1	NN	NN
Abdurraham et al, 1982[13]	No	NA	NA	NA
Kaplan et al, 1985[14]	Yes	0.2	0	0
Murata et al, 1985[15]	No	NA	NA	NA
Glucose				
Bryan et al, 1966[3]	NP	2.6	NN	NN
Belliveau et al, 1970[10]	NP	4.0	NN	NN
Bates and Yellin, 1972[11]	No	NA	NA	NA
Korvin et al, 1975[12]	Yes	1.1	NN	NN
Olsen et al, 1976[16]	No	NA	NA	NA
Abdurraham et al, 1985[13]	No	NA	NA	NA
Domoto et al, 1985[17]	No	NA	NA	NA
Kaplan et al, 1985[14]	Yes	0.9	0	0

NA = not applicable, NN = not noted, NP = not possible to determine from methods discussion

*See methods section for a description of our criteria.

for many clinical situations, and training in these should be incorporated into medical education.[26]

Although we cannot determine absolutely whether current test-ordering behavior at our institution represents true screening or simply reflexive test ordering, we know that neither practice provides clinically useful information. "Completeness" should no longer be considered a reason for doing these tests.

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DAVID GREER

1943-1987

Managing Editor, THE WESTERN JOURNAL OF MEDICINE, 1974 to 1987

Clinical Medicine

Space Medicine—A Review of Current Concepts

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Space medicine deals with the branch of research involved with the adaptation of humans to the unique environment of space. More than 100 people have traveled in space. The day will come when some human beings will spend all their time in space. Medical problems encountered in space, such as motion sickness, negative nitrogen and calcium balance, anemia and radiation exposure, are issues that already affect medical practice outside aerospace medicine.

(Vasquez TE, Pretorius HT, Rimkus DS: Space medicine—A review of current concepts. West J Med 1987 Sep; 147:292-295)

To reach space, travelers must first endure acceleration to a velocity of 17,900 miles per hour to attain the earth's orbit. A final velocity greater than 25,900 mph is needed to escape the earth's orbit. The older launch vehicles produced high peak accelerations, reaching 7 G (1 G = earth's gravity field) during the Gemini/Titan launch.[1] In contrast, the space shuttle does not exceed 3 G at maximum acceleration.[2(p 53)] To provide increased tolerance to high acceleration, the astronauts are positioned reclining relative to the path of the spacecraft. In this optimal position, tolerance to acceleration (transverse) is limited by chest pain and compromised respiration related to the increased effective weight of the chest wall.[3] The vital capacity decreases by half[3] at 6 G, and respiration is further decreased by ventilation-perfusion mismatching and atelectasis that develop rapidly in the dependent, posterior portions of the lungs.[3-5]

When the rocket motors stop and a spacecraft enters orbit, astronauts experience weightlessness—in actuality, a microgravity equal to 0.001 to 0.00001 G and mainly only the lower 10% of this range, except when the spacecraft motors are on.[6]

Space Motion Sickness

Once in orbit, and usually within the first several hours, symptoms such as motion sensitivity, malaise, lethargy and brief episodic vomiting will develop in about half of the crew.[7] These symptoms define a clinical syndrome now called space motion sickness. Specific causes of space motion sickness are uncertain, though it was not reported[7-9] among any of the early American astronauts in the Mercury or Gemini crews (19 men, 7 of whom flew twice). Similarly, space motion sickness was only reported once among the first six Soviet cosmonauts.[7] These results may relate partly to a reluctance of early astronauts to report any adverse reactions, although other differences between the early and later missions are also pointed to as etiologic of space motion sickness.

For example, a principal role of increased head motion is postulated as a cause of space motion sickness,[10] and the early astronauts, in their smaller spacecraft, had limited head motion. In favor of this interpretation, the Russian cosmonaut Titov, the second Soviet spaceperson, whose case may be considered the first documented case of space motion sickness, specifically noted an association between rapid head movements and malaise.[11] Also, five of six crew members in Apollo 8 and 9 reported symptoms of space motion sickness during a period when head motion was less restricted and, unfortunately, perhaps actually encouraged.[6,12]

On the other hand, despite reports of benefit from a head-restraint device developed for the Soviet Salyut 6 crew, there appeared little decrease in the overall attack rate of space motion sickness among cosmonauts who occupied the Salyut 6 space station, this rate being 12/27.[7] Neither has the awareness of a possible role of head motion made much difference in the attack rate among American astronauts after Apollo, which was 10/24 on the Skylab, Apollo Soyuz test project and space shuttle missions up until 1982.[7]

Clearly, the exact cause of space motion sickness and effective ways to combat it are as yet unknown. In most cases it seems to be a self-limited sickness that resolves within several days. Symptoms sometimes last up to six days, however, and in at least one case (the scientist astronaut on Apollo), even longer.[12] Efforts to predict a particular sensitivity to space motion sickness or to train astronauts to prevent it have so far had only limited success,[12] although it is often thought that evidence of sensorineural vestibular changes might be pertinent.[13] One definite sign of space motion sickness that has perhaps had inadequate emphasis is the absence of bowel sounds during it and the return to a normal or even hyperactive state in those recovering from the sickness.[14]

Musculoskeletal System

The musculoskeletal system has evolved in a 1-G environment. Weightlessness greatly reduces the muscular force required to maintain posture. Russian cosmonauts wear a "penguin" suit during waking hours on long missions.[15] This suit contracts the wearer into a fetal position unless muscular force is applied against its elastic fibers; it thus mimics the "load" of gravity in an effort to prevent the muscle atrophy that is a consequence of space travel.[15]

Astronauts experience persistent negative nitrogen balance during spaceflight. Urinary nitrogen concentration is substantially increased during spaceflight, along with urinary amino acids, including 3-methylhistidine.[13] Various exercise regimens so far used on space missions to limit muscle at-

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rophy include walking on a treadmill, bicycle ergometry, electrostimulation and elastic resistive devices.[7] While such techniques, particularly those concentrating on the use of the major muscle groups, do have an effect in reducing muscle atrophy, they are incomplete,[6] and a period of readjustment on returning to the 1-G environment is still required.

Bone and Calcium Metabolism

Under microgravity conditions increased bone resorption occurs. Astronauts go into negative calcium balance early and continuously throughout a space mission.[6,15] They have a reduced net intestinal absorption of calcium as shown by an increased fecal calcium content.[6] The amount of calcium lost per month of exposure to microgravity is about 4 grams, or 0.4% of the total body calcium.[6] Failure to restore lost calcium may increase the risk of clinical osteoporosis with advancing age.[15] Providing that problems related to cumulative radiation exposure (to be discussed later) can be resolved, the astronauts' negative calcium balance could be a limiting factor in terms of the total time tolerable for human spaceflights.

For this reason—and of course on account of its increasingly recognized significance as a clinical problem on earth—much effort is currently expended on research on calcium metabolism and osteoporosis. A specific factor perhaps relevant to the environmental osteoporosis developing in space is the presence of a natriuretic factor in the urine of subjects immersed in water.[16] Of course, this factor may be the atrial natriuretic hormone.[6,17] The recent report of a major effect of the atrial natriuretic hormone on cyclic guanosine monophosphate formation in osteoblasts[18] is certainly of interest because cyclic nucleotides are important regulators of cellular function. While osteopenia occurs especially in estrogen-deficient women, it develops with age in men as well,[19] and concentrations of the atrial natriuretic polypeptide also increase with age.[20] Nonetheless, the role of cyclic guanosine monophosphate in osteoblast function remains to be established, and other factors, such as elevated cortisol values[15] in astronauts, may also contribute to a negative calcium balance. Despite intensive research there is no established explanation for nor an effective countermeasure against the environmental osteoporosis due to microgravity conditions.

Cardiovascular Changes

Along with "unloading" the musculoskeletal system, weightlessness abolishes the normal hydrostatic pressure gradient in the cardiovascular system.[6,21] In the absence of this gradient, venous pressures become equal throughout the body. Several liters of fluid then redistribute from the ordinarily dependent lower portions of the body toward the thorax and head.[6] Thirst is suppressed by an apparent intravascular fluid increase. Although urine production is slightly decreased, the astronauts suffer a net loss of fluid during the first days of a space mission. Up to two liters of body fluid are excreted within a few days of weightlessness,[6] after which the body reaches a new state of cardiovascular hydrostatic equilibrium. Astronauts do have prominently distended jugular and cephalic veins throughout a flight[6,21]; these distended veins, however, are not a direct measure of the central venous pressure in the absence of a gravitational field of reference, and definitive measurements to determine if the central venous pressure is increased in space are still to be done.

Cardiovascular deconditioning in space may result from the reduced cardiac workload during weightlessness. Inspiratory and expiratory chest radiographs gated to the cardiac cycle among 61 US astronauts taken before and after space missions showed a mean decrease of 0.018 in their cardiothoracic ratios,[22] which is of uncertain statistical significance. Echocardiography of several space shuttle crew members before, during and after a space mission showed changes in cardiac anatomy.[23] On the first day of a space mission, ultrasound measurements show that the left side of the heart increases in size while the right side unexpectedly decreases,[23] as does the central venous pressure according to one source.[2 (p 151)] During the second day of the space mission, the entire heart becomes smaller than preflight and does not return to preflight size for at least one week postflight.[23] On returning to earth, several liters of fluid sequestered in the legs cause temporary orthostatic hypotension and intolerance of an upright posture. Consuming fluids immediately before returning from orbit and inflating anti-G suits to prevent venous pooling in the lower extremities are not entirely successful in eliminating this problem.[6]

The fluid shifts observed on space missions might be expected to cause temporary changes in the total blood volume and hematocrit. The initial fluid overload may cause passive congestion and sequestration of erythrocytes in the liver, spleen and lungs. Erythropoiesis is probably suppressed by 10% to 15% rather than completely suppressed, as shown by the continued production of reticulocytes, continued use of iron and eventual equilibration of red cell mass at about 90% of preflight levels.[24]

In vitro erythrocytes under zero gravity do not show evidence of crenation, burr cells or other unusual shapes.[25] These data are in contrast to reported changes in erythrocyte morphology in several astronauts in whom significant (up to 10% to 15%) echinocytes developed temporarily during spaceflights, and rouleaux have also been seen.[26] Erythrocyte mass is reduced by 10% to 15% during space travel.[24] About four to six weeks are required after space travel for the erythrocyte mass to return to normal. The cause of the anemia related to space travel is currently unknown.

Radiation Exposure

Cosmic rays and charged particles originating from the sun and outer space continually strike the earth's atmosphere. Many of these cosmic particles are trapped by the earth's magnetic field forming the Van Allen radiation belts. Among the many environmental pollutants, the ability to directly quantitate even low levels of radiation has allowed accumulation of much evidence relating to the medical risks of radiation exposure. Persons leaving the shelter of the earth's atmosphere increase their radiation exposure from the usual average background level of about 125 millirems per year—approximately 40 mrem derived from cosmic rays at sea level, 60 mrem from the ground and structural building materials and 25 mrem from water, food and air.[27] While such usual background levels are thought to have minimal adverse effects, there remains much uncertainty about the cumulative effect of low levels of radiation. The consensus is that an assumption of a linear dose-response behavior for radiation probably overestimates the effects of low levels of radiation and is therefore a safe or "conservative" estimate appropriate for radiation safety considerations.[28]

At radiation levels significantly higher than the 125 mrem background range, biologic and medical effects become real

rather than theoretic. Radiation by its very nature tends to produce multisystemic effects, which are grouped into the temporal considerations particularly relevant to exposure during space travel.

Acute Radiation Effects

Exposure of humans to radiation in the range of hundreds of rems results in acute radiation sickness. A whole-body exposure of 400 to 500 rem would kill about half of exposed personnel within 30 days.[28] The initial signs and symptoms include nausea and vomiting. With the passage of time (days to weeks) the entire hematopoietic system becomes depressed. Complications include recurrent infection due to neutropenia, diarrhea and epilation.[28] A higher exposure in the 10,000-rem range would be lethal to humans within 24 hours due to central nervous system damage.[28]

To date, the highest recorded radiation exposure to a United States astronaut is 7.8 rad on the 84-day voyage of Skylab 4.[7] This level is far below that necessary to produce clinically evident acute effects. Significant exposure to the Van Allen radiation belts, such as might occur with a spacecraft in a polar orbit, an atmospheric nuclear explosion or increased solar (sunspot) activity, would be necessary to produce doses in the 100-rem range.

Acute effects of radiation on sensitive tissues and metabolic systems occur at much lower doses. These effects include decreased function and death of lymphocytes, which are probably the cells in the body most sensitive to radiation, and cumulative damage to spermatogonia, which is evident after as little as 3 mrem in mice.[28] The sum of such effects is thought to produce only subclinical disease initially; but in some cases, such as the damage of nucleic acids, may produce significant biologic effects at a later time.

Long-term Effects

The long-term effects of radiation exposure include increased risk of genetic mutation, neoplastic disease, cataract formation and a decreased life span.[28] The leukemia risk with radiation is estimated to be in the range of 0 to 2 cases per million per rad.[29(p239)] While relatively low, this risk is thought to double the normal leukemia risk at a cumulative exposure of about 400 rem.[7] The risk of thyroid carcinoma and, to an even greater extent, benign thyroid nodules is significantly increased with radiation exposure of the amounts already encountered in space, because there is good evidence that the threshold level (if it exists) for radiation-induced thyroid disease is very low.[30(p775)] The United States has attempted to limit crew exposure to 25 rem per mission (whole body), with limits of 75 rem per year and a 400 total rem limit per astronaut.[7] In addition to nearly doubling the projected risk of the most common malignant disorder (leukemia), these levels are thought to amount to a decrease in life expectancy of 0.5 to 3 years.[31(p69)]

Life Support

Nutritional requirements in weightlessness appear similar to those on earth. The initial caloric provisions have progressively increased as astronauts have become more mobile and adept at working in space. Currently the daily caloric allowance is about 3,000 kcal.

At a typical space shuttle orbital height of 300 km (186 mi), atmospheric pressure is negligible. To provide a livable atmosphere for the crew, a spacecraft is sealed at launch. Thereafter, oxygen is added to the system to replenish consumption and leakage; carbon dioxide is extracted.

From the very beginning of the space era, Russian spacecraft used a two-gas environmental system designed to maintain an earthlike (sea level) atmosphere.[6] Because of the increased weight of a two-gas life support system, early US spacecraft used 100% oxygen. The Skylab atmosphere used 70% oxygen and 30% nitrogen at 260 millibars. The space shuttle is the first US spacecraft to maintain an earthlike atmosphere similar in both composition and pressure—760 mbar, 20% oxygen, 80% nitrogen. Carbon dioxide is removed from the shuttle environment by lithium hydroxide cartridges. Water vapor (humidity) and temperature (18°C to 27°C [64°F to 80°F]) are also strictly regulated by the shuttle environmental control system. Astronauts don space suits that provide them with portable life support to conduct extravehicular activity. Maximal flexibility of the space suit has required a reduction in pressure to 222 mbar from the shuttle cabin pressure of 1 atmosphere. To prevent decompression sickness, shuttle astronauts first lower the cabin pressure to 527 mbar at least 12 hours before extravehicular activity. This reduction in pressure reduces tissue nitrogen. Those astronauts slated for the extravehicular activity then breathe 100% oxygen for 40 minutes while in their space suits to wash out traces of nitrogen. Finally, the suit is reduced to a pressure of 222 mbar in the airlock.

Early spacecraft had primitive waste-collecting facilities. The space shuttle has a modern waste-collecting system with separate assemblies for urine (cup and tube urinal) and solid waste (commode). This system is designed for both sexes for use in either zero or one gravity.

Only the future can answer many of the currently unanswered questions involving space medicine. The current record of 236 days, 21 hours, 49 minutes of continuous time in space was set by Soviet cosmonauts Kizim, Solovyov and Atkov. Records exist to be broken.

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Cosmetic Reactions to Artificial Fingernails

I SEE ONE OR TWO PATIENTS every day with acrylic nail problems. Here is basically what happens with an acrylic nail: A woman applies a topical irritant chemical on the outside of the nail. If an irritant chemical is applied to the outside of the skin anywhere, dead scale piles up. When applied to the surface of the nail, dead keratin begins to pile up underneath the nail—a normal response to an irritant substance. If a woman with acrylic nails puts her hands into water, all this dead material that is underneath the nail is soaked out, and a pocket occurs that is an ideal place for water to accumulate and stay. The main way the skin degerms itself is by being too dry for the survival of organisms. When there is a pocket underneath the nail, all kinds of garbage organisms grow under there—*Pseudomonas, Aspergillus* and others. How do I treat these? Basically, if a patient is having trouble with discoloration from all the various organisms, I recommend putting a drop of clindamycin phosphate topical solution (Cleocin T, for example) underneath the nail two times a day. This dries it out and also helps kill off all the saprophytic organisms. The other treatment I usually use is triamcinolone acetonide (Kenalog) spray or one of the other steroid sprays. I advise patients to take the spray with the scalp adapter and cut it short so it can be sprayed right up underneath the nail; this gets a small amount of steroid there to cut down on the irritation and a little antibiotic to cut down secondary infection. This is usually a one-visit procedure after I have explained to a patient what is going on and what to expect.

Silk nails are coming in now. I see very little problem with silk nails except when they break off. Then a super strength, fast-drying glue is used to put them back on, which again causes numerous allergic reactions.

—ORVILLE J. STONE, MD

Extracted from *Audio-Digest Family Practice*, Vol. 35, No. 16, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Evaluation of the First 300 Patients Treated at an Outpatient Center for Male Sexual Dysfunction

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A comprehensive multidisciplinary evaluation was carried out on 300 outpatients seen consecutively at a specialized impotence center. Psychologic evaluation was coupled with the use of contemporary diagnostic modalities. Nocturnal penile tumescence testing, penile vascular studies, pharmacologic diagnostic testing and dynamic infusion cavernosography have been used advantageously. In addition to psychologic counseling for all treatment categories, treatment alternatives have included hormonal and pharmacologic agents and penile prosthetic implantations.

(Ellis LR, Nellans RE, Kramer-Levien DJ, et al: Evaluation of the first 300 patients treated at an outpatient center for male sexual dysfunction. West J Med 1987 Sep; 147:296-300)

Increasingly, urologists are becoming the primary source for information and treatment regarding impotence. But the typical busy urologic and general medicine practice setting does not lend itself well to the measured evaluation necessary for optimally managing this problem. An awareness of the promising alternative of multidisciplinary impotence treatment centers elsewhere led to the establishment of the Northwest Center for Impotence in October 1984.[1] We present the results of the diagnostic evaluations and therapeutic techniques used with 300 outpatients evaluated consecutively at the center since its inception.

Methods

The center was initially conceived as a collaborative venture, embracing both urologic and psychologic disciplines to provide case-specific treatment plans. An exceptionally well-qualified registered nurse coordinator was recruited, and provisional agreement was subsequently achieved among urologists and two groups of certified sex therapists. Initial patient contact with the nurse coordinator to outline the purpose and overall management approach has been pivotal to successful clinic efforts. Comprehensive patient education and an awareness of support services have been achieved. Instructional videotape material has been used extensively throughout diagnostic and treatment phases. Clinic urologists have employed cost-effective, focused diagnostic testing followed by the institution of selected medical or surgical therapies or referrals for appropriate counseling.

Initially, a separate physical location was considered desirable to provide the most confidential patient care setting. After 18 months of free-standing operations, however, subsequent disadvantages were not noted with reconfiguration into a full-service urologic office suite.

The center's development also involved the establishment and ongoing coordination of an impotence support group in collaboration with the local hospital. Monthly meetings have been held with both patients and partners attending either confidential, closed group sessions or public forums featuring selected speakers. Increased public awareness and acceptance have evolved.

General Evaluation

After first reviewing the extensive preliminary patient questionnaire, clinic urologists take a comprehensive history and do a physical examination with special attention to cardiovascular, neurologic or psychosexual disorders. Laboratory evaluations including blood glucose, luteinizing hormone, prolactin and testosterone levels focus on endocrinologic manifestations such as diabetes mellitus or disorders of gonadal function. The laboratory screen also evaluates renal, liver and thyroid function.

Special Vascular Testing

In addition to a careful vascular history and physical assessment, the noninvasive Parks vascular minilaboratory apparatus with a 9.5-mHz Doppler probe has been used extensively. A consistent and reproducible measurement of the penile pulse volume, with Doppler and photoplethysmographic systolic occlusion pressure testing, has provided an accurate evaluation. Normal ratios of penile artery to brachial systolic occlusion pressures (penobrachial index, or PBI) are defined as greater than 0.75; PBI values of 0.72 to 0.75 are borderline, and less than 0.72 are considered abnormal.[2-4] When arterial or venous lesions have been suggested by noninvasive test results, an evaluation protocol has been used (see Figure 1) for further confirmation. Papaverine diagnostic screening has been used judiciously, usually involving the intracorporeal administration of 1 ml of a standardized papaverine-phentolamine mixture containing 30 mg papaverine hydrochloride and 0.83 mg phentolamine mesylate.[5] Selected patients with possible arterial lesions or the pelvic steal syndrome have been evaluated by phalloarteriography. Patients with an adequate arterial inflow and adequately achieved but poorly sustained erections have also been studied by dynamic infusion cavernosography to evaluate a possible venous insufficiency.[6] Cavernosography in the normal flaccid state reveals

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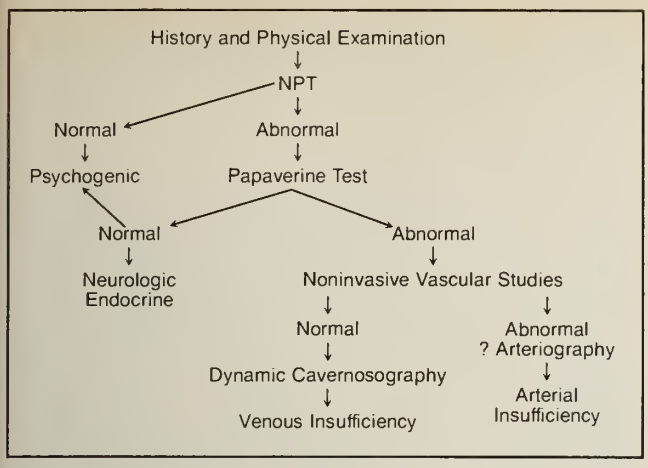

Figure 1.—The graph shows the protocol used at the Northwest Center for Impotence, Bellevue, Washington, to evaluate male sexual dysfunction. NPT = nocturnal penile tumescence

rapid filling of internal and external pudendal venous systems and the prostatovesical plexus. After infusion of a saline solution or artificial erection with the use of papaverine, occlusion of venous return is seen in normal subjects, but not in cases with measurable degrees of venous insufficiency.[7]

Neurologic Assessment

A thorough general neurologic examination is carried out with special attention to specific aspects of sacral innervation. On occasion, formal urodynamic studies and sacral reflex latency time determinations have been done in collaboration with the hospital electroencephalographic laboratory. Abnormal sacral neurologic function in cases such as multiple sclerosis, diabetes mellitus or chronic back syndromes are denoted by latency times of greater than 45 milliseconds.[8] Dorsal penile nerve sensory function has been additionally assessed through routine biothesiometer testing of vibratory sensation as described by Levine and Sax.[9]

Psychosocial Assessment

Psychologic evaluations are conducted by the clinic coordinator or collaborating certified psychologist-psychiatrist personnel. Before referral for psychologic assessment, a Minnesota Multiphasic Personality Inventory profile has occasionally been done.[10,11] Selected patients have been put on short-term counseling, sex therapy or formal psychotherapy programs. A protocol has also been developed to evaluate the efficacy of papaverine-phentolamine injection therapy coupled with psychotherapy for well-selected psychogenically impotent patients. This study will be the subject of a future report.

Nocturnal Penile Tumescence Studies

Evaluation of nocturnal penile tumescence testing is routinely done either with snap-gauge testing or by take-home monitoring with the Rigiscan tumescence and rigidity monitor. When results of snap-gauge screening have been inconclusive or greater definition is required, Rigiscan monitoring for one or two nights has been successfully used. Concurrent tumescence and rigidity measurements have been achieved without the need of extensive laboratory testing or technician monitoring. The Rigiscan data logging unit has been used in conjunction with a software program operated through an IBM PC microcomputer for processing and printing data. Each nocturnal event is graphically displayed to allow evaluation of both penile tip and base tumescence and rigidity over time.[12]

Results

Patients have been categorized into four diagnostic groups: organic, primary organic, psychogenic and primary psychogenic.

Organic

Organic impotence has been defined as a lack of maximal or partial rigid erection preventing vaginal penetration, associated with identifiable medical causes. Prominent psychologic factors are absent and nocturnal penile tumescence testing has been confirmatory.

Primary Organic

In this category, some variability and discrepancy of nocturnal penile tumescence test results have been noted, with relevant psychologic factors having been present. The organic medical condition or treatment is considered predominant, however, as the cause of erectile failure.

Psychogenic

In this situation, erectile activity sufficient for penetration has been seen with nocturnal tumescence testing, and psychosexual evaluation has elicited a notable predominance of psychological factors.

Primary Psychogenic

Psychologic factors are considered preeminent in this category, but are coupled with organic disease of lesser importance to the erectile dysfunction.

Of the total group of 300 patients, 149 (50%) had organic processes, 28 (9%) organic disease with associated psychologic contributions, 94 (31%) purely psychogenic causes and 29 (10%) had psychogenic predominance coupled with organic diatheses of lesser importance (Table 1). Ages in the series ranged from 25 to 85 years, with organic diagnoses increasing with age, peaking in the 60- to 69-year age group. Considerable psychogenic impotence was seen in older age groups as well. In all, 39% of patients were single. Psychogenic causes were twice as common in the single group.

Organic Impotence

Organic causes of impotence are outlined in Table 2. A predominance of vascular-related, neurologic and endocrine disorders has been seen. Penobrachial indices are lowest in vascular, diabetic, postsurgical and trauma cases. The diabetic case incidence is only 7%, lower than that reported in most series.[13] Relative to the incidence, however, the rate of penile implantation was quite high in this group (Table 3).

Psychogenic Impotence

Thus far, 55 patients have received counseling, 18 have been referred for sex therapy and 6 have initiated significant psychotherapy programs. During clinical evaluation it has been found that patients with persistent impotence ultimately display psychologic manifestations even if physical factors predominate. In addition, psychogenic factors persist after organic disease is treated. Even in apparently obvious psychogenic cases, subtle organic factors can be etiologically relevant.

Penile Vascular Studies

Penile vascular studies were done on 203 patients and included plethysmographic recordings of penile pulse volume, photoplethysmographic and Doppler penile blood flow determinations with penobrachial index calculations. The PBI decreased progressively with increasing age. An excellent correlation existed in this series between Doppler PBIs lower than 0.72 and abnormal pulse volume recordings. Photoplethysmography was more sensitive than Doppler for PBI determinations but carried a higher false-positive rate. Doppler penile pressure measurements were technically not obtainable in all patients, however. Rarely is the penobrachial index obtained by photoplethysmography higher than the Doppler PBI; consequently, if the PBI by photoplethysmography is greater than 0.76, a Doppler study is not required. Photoplethysmography and pulse volume recordings are reliable and somewhat more convenient to do than Doppler recordings, but data must be interpreted collectively in assessing overall penile vascular status.

Nocturnal Penile Tumescence Studies

Snap-gauge testing and Life-Tech or Rigiscan nocturnal penile tumescence monitoring were used. Of the total series, 63% were tested with some form of penile tumescence monitoring (Table 4). Of the evaluated group (191 patients), 56% had screening accomplished with the snap-gauge device and 46% by nocturnal penile tumescence monitoring. An overlapping group of 8% was tested by both techniques. Snap-gauge testing as an isolated measure of rigidity was useful with relatively acceptable correlations for both organic and psychogenic cases. An organic false-positive rate of 20% was obtained, however; the psychogenic false-negative rate was a more acceptable 4%. A snap-gauge accuracy of 96% for psychogenic cases and 80% for organic causes was noted (Table 5). Nocturnal penile tumescence monitoring data displayed an organic false-positive rate of 22% and a psychogenic false-negative rate of 8%. Therefore, the accuracy of penile tumescence monitoring with psychogenic cases was 92% and 78% for organic cases (Table 5).

TABLE 1.—*The Northwest Center for Impotence Series, N=300*

Diagnostic Group	Patients	
	Number	Percent
Organic	149	50
Primary organic	28	9
Psychogenic	94	31
Primary psychogenic	29	10
Total	300	100

TABLE 2.—*Organic Causes of Impotence, N=300*

	Patients		Average PBI
	Number	Percent	
Vascular	49	16	0.59
Neurologic	27	9	0.81
Diabetes mellitus	20	7	0.69
Endocrine	17	6	0.79
Drug related	7	2	0.83
Venous insufficiency	14	5	0.80
Peyronie's disease	5	2	0.90
Postsurgical	5	2	0.69
Posttraumatic	3	1	0.62
Infection	2	1	0.89
Primary organic	28	9	0.73
Total	177	60	

PBI=penobrachial index

TABLE 3.—*Penile Implants*

Cause of Impotence	Inflatable	Malleable	Hydroflex	Total
Diabetes mellitus	3	2	1	6
Vascular	4	2	1	7
Peyronie's disease	2	0	1	3
Postsurgical	0	0	1	1
Posttrauma	2	0	0	2
Neurogenic	3	1	0	4
Mixed	4	0	2	6
Total	18	5	6	29

TABLE 4.—*Percentage Having Nocturnal Penile Tumescence Studies, N=191*

Test	Patients	
	Number	Percent*
Snap gauge	107	56
Monitor	88	46

*Some patients were tested by both techniques.

TABLE 5.—*Nocturnal Penile Tumescence (NPT) Testing Results**

Snap Gauge

Patient Group	Test Results		
	Positive	Partial	Negative
Organic	3	15	43
Primary organic	2	6	5
Psychogenic	17	7	1
Primary psychogenic	2	6	1
Totals	24	34	50

NPT Monitor

Patient Group	Normal (Pos)	Borderline	Abnormal (Neg)
Organic	4	3	42
Primary organic	2	2	6
Psychogenic	17	3	0
Primary psychogenic	4	1	4
Totals	27	9	52

Neg=negative, Pos=positive

*In these studies, a "positive" result indicates a normal test, a "negative" result indicates the presence of an abnormality

TABLE 6.—*Drugs Used in Medical Treatment of Impotence**

Drug	Patients, No.
Isoxsuprine hydrochloride (Vasodilan)	44
Yohimbine (Yocon)	18
Fluoxymesterone (Halotestin)	10
Testosterone cypionate (Depo-Testosterone)†	50
Antibiotics	7
Papaverine hydrochloride‡	53

*Some patients received more than one drug
†Administered intramuscularly.
‡Administered intracorporeally

TABLE 7.—*Androgenic Replacement Therapy*

Diagnostic Group	Patients, No.	Serum Testosterone Level, Range, ng/dl	Average PBI	Results*
Testosterone Given Orally (N=10)				
Organic	7	249 to 373	0.80	+(5) −(2)
Primary organic	1	359†	0.66	±(1)
Psychogenic	1	328†	0.87	−(1)
Primary psychogenic	1	439†	0.88	−(1)
Testosterone Given Intramuscularly (N=50)				
Organic	22	67.5 to 400	0.74	+(16) ±(2) −(4)
Primary organic	18	190 to 384	0.77	+(8) ±(2) −(8)
Psychogenic	3	468 to 532	0.81	+(1) −(2)
Primary psychogenic	7	230 to 398	0.78	+(4) ±(3)

PBI=penobrachial index, +=positive, −=negative, ±=equivocal

*Numbers in parentheses represent number of patients.
†One serum testosterone concentration was determined for each patient.

TABLE 8.—*Oral Pharmacologic Therapy*

Diagnostic Group	Patients, No.	Testosterone Level, Range, ng/dl	Average PBI	Results
Isoxsuprine Hydrochloride Therapy (N=44)				
Organic	25	247 to 820	0.62	+(4) ±(4) −(17)
Primary organic	7	284 to 612	0.72	+(4) −(3)
Psychogenic	1	...	0.95	−(1)
Primary psychogenic	11	325 to 830	0.78	+(5) ±(4) −(2)
Yohimbine Therapy (N=18)				
Organic	3	339 to 473	0.77	−(3)
Primary organic	2	509 to 612	0.68	−(2)
Psychogenic	12	325 to 726	0.86	6/12+
Primary psychogenic	1	511	0.75	±(1)

PBI=penobrachial index, +=positive, −=negative, ±=equivocal

TABLE 9.—*Intracorporeal Pharmacologic Therapy, N=53**

Papaverine hydrochloride, 30 mg, + phentolamine mesylate, 0.83 mg
1 ml or less administered
2 ×/wk or 10 ×/mo
Careful monitoring and follow-up with liver function tests
Observe for hematuria, infection, priapism
Need extensive informed consent

*The following response to therapy was noted. 62% responders, 17% partial responders, 21% nonresponders.

TABLE 10.—*Complications of Penile Implant Therapy (N=29)*

Complication	Type of Implant: Inflatable	Hydroflex	Malleable
Loose connectors	2	...	...
Pump malfunction	1	...	...
Cylinder herniation	1	...	...
Hematoma	2	0	0
Infection	1	0	0

Sacral Reflex Latency Testing

Selected patients had sacral reflex latency testing with fairly conclusive results—that is, latency times greater than 45 ms. Sensory threshold monitoring of vibratory appreciation has recently been tested routinely with the biothesiometer. According to Goldstein, useful information can be obtained in cases of a dorsal penile neurosensory deficit (I. Goldstein, MD, Department of Urology, Boston University School of Medicine, oral communication, 1985).

Hormone Determinations

Prolactin values were measured frequently, but were elevated on only two occasions, with no significant pituitary disease present on follow-up testing. Repeat determinations of testosterone levels of patients taking androgens by mouth consistently showed further reductions of already low testosterone values, thought to be on the basis of biofeedback suppression of gonadotropins and endogenous testosterone production, together with the concurrent presence of androgenic metabolites other than testosterone.

Medical Therapy

Medical treatments used at the center are noted in Table 6. Oral and intramuscular administration of androgen provided optimal results, with complete responses of 60% and 48%, respectively (Table 7), but overall numbers are small. A complete response rate to the use of isoxsuprine hydrochloride is low (29%) and unpredictable. Giving yohimbine provided no benefit in patients with organic problems, but it was of significant short-term benefit (38%) to patients with psychogenic causes, suggesting a strong placebo effect (Table 8). Results with the use of combinations of yohimbine and isoxsuprine have also been unimpressive.

The most notable medical therapy has been with the administration of papaverine and phentolamine intracorporeally. In all, 53 patients have been treated for periods of as long as a year with a 62% complete response rate, partial response 17% and no response 21% (Table 9). Iatrogenic priapism has been reversed on four occasions with corporeal irrigation and injections of dilute α-metaraminol solution. Papaverine therapy has been discontinued in two patients who had cavernosal or tunical focal fibrosis. A focal necrotic superficial eschar of the glans penis developed in one patient after injection and the drug therapy was discontinued.

In cases of impotence related to cardiac drug usage, dosage adjustments or a switch to more optimal drugs is coordinated with referring physicians. Smoking cessation, reducing alcohol consumption and other beneficial life-style changes are strongly advocated.

Surgical Therapy

Of the 300 patients, 29 (10%) received penile implants with either Malleable, Hydroflex and AMS or Mentor inflatable penile prostheses. The age range was 33 to 75 years, with a peak incidence of implantation occurring between 50 and 70 years of age. Patients having a vascular cause constituted the largest single group. One venous ligation procedure was accomplished with inconclusive results, but no penile revascularizations were done. As an adjunct to surgical treatment, on occasion the surgical isolation bubble system has been used with good results.[14] The surgical complication rate was low, with specific adverse events noted in Table 10.

Discussion

There are numerous advantages inherent in providing a multidisciplinary approach for the treatment of impotence. Prompt, coordinated evaluation of both organic and psychogenic factors can be initiated in a unified care setting. The relative importance of certain factors can be best ascertained with the close collaboration of and communication with involved urologists and such persons as consulting endocrinologists, psychiatrists and psychologists.[15,16] A framework for clinical research projects and data analysis can also be provided. Networking with similar groups throughout the country is feasible. Patients and their families have been quick to recognize the level of interest and support provided and respond accordingly. The most optimal situation involves close physical proximity of health care professionals in a center, although successful operations are possible among dispersed personnel.

The role of clinic coordinator cannot be overemphasized. This person provides an initial contact point and in many respects sets the necessary tone for successful ongoing relationships. Adjunctively, a full spectrum of educational audiovisual materials is crucial to enhancing patient levels of awareness and understanding, coupled with reinforcing discussions with center personnel. Clinic coordination with patient support groups has also been influential in the context of the overall program.

Penovascular studies can be helpful in assessment and have been used with increasing frequency by many investigators.[2-4] They have been accurate and of diagnostic benefit when interpreted selectively.

The selected use of Rigiscan testing has provided considerable current refinements to nocturnal tumescence testing. The take-home monitor system is cost-effective and adaptable to the clinic setting. Considerable assistance has been noted when interpreting findings suggesting venous insufficiency, uncoupling or dissociation. It is important to interpret an entire tracing sequence rather than focusing on single indices such as maximal rigidity.

Nocturnal penile tumescence testing can show individual and methodologic differences and therefore cannot be used as the sole determinant for differentiating organic from psychogenic impotence. But it has been a good screening tool. Rigiscan testing has overcome the nonlinearity problem seen with other available nocturnal tumescence monitors.

During the course of clinic evaluations and therapeutic trials, certain treatment methods have shown greater promise. The selected use of injectable or oral androgens is supported by available data in this study. Firm conclusions cannot be reached regarding such drugs as yohimbine and isoxsuprine, for they are of unpredictable benefit. Papaverine injection therapy continues to show short-term promise without a major risk of side effects. Of particular interest is the multiplicity of applications for papaverine therapy. The technique has been used diagnostically to differentiate cases of venous insufficiency and therapeutically to "prime the pump" in conjunction with psychotherapy. In its more standard application, papaverine injection therapy has provided substantial benefit for the management of neurogenic impotence, mild to moderate arterial vasculogenic impotence and mild cases of penile venous insufficiency.

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Recent Advances in the Treatment of Duodenal Ulcer Disease

A Surgical Perspective

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Chronic peptic ulceration is a disease process in transition. During the past two decades, the disease has changed in its incidence, in its presentation and in its medical consequences. The pathogenesis of acid-peptic disease has been the major focus of numerous investigations, and major advances in understanding basic gastric physiology have led to specific and increasingly effective therapeutic approaches. With the introduction of H_2-receptor antagonists, the treatment of peptic ulceration has been radically altered, and many new therapies await clinical trial. Surgeons treating gastroduodenal ulceration will require greater knowledge of gastric physiology and an increasingly refined appreciation of both the power and limitations of various medical and surgical therapies.

(Mulholland MW, Debas HT: Recent advances in the treatment of duodenal ulcer disease—A surgical perspective. West J Med 1987 Sep; 147:301-308)

Peptic ulceration is a disease in the midst of remarkable changes. During the past several decades, duodenal ulceration has changed in its frequency and in its medical and economic consequences. Concerted efforts by scientists from a variety of disciplines have produced major advances in the understanding of basic gastric physiology, and because of these advances, increasingly specific and effective therapies have been developed. The treatment of duodenal ulcer has already been radically altered, and a large number of new therapeutic agents still await clinical trial. The role of surgical treatment of peptic ulceration is being redefined.

Physicians treating duodenal ulceration require an increasingly sophisticated appreciation of gastric physiology, of pharmacology and of the usefulness and limitations of surgical therapies. In this review we will emphasize the changing nature of peptic ulcer disease, as viewed from a surgical perspective. We examine the physiology of gastric acid secretion and the pathophysiology of peptic ulceration. A practical guide to combined medical-surgical therapy will be offered for differing clinical circumstances.

Epidemiology

The incidence of duodenal ulceration has been declining in the United States for the past three decades. The data that support this contention come from a wide variety of sources—from studies of military personnel, from the Veterans Administration and from physician surveys.[1-3] In addition to a decreasing incidence, the treatment of peptic ulcer has become less hospital-oriented. Hospital admission rates for duodenal ulcer have decreased sharply. In the decade of the 1970s, hospital admissions in the United States for the treatment of duodenal ulcer dropped by 40%.[4] The fall in duodenal ulcer admissions has been broadly paralleled by falling ulcer-related mortality rates.

When examined more closely, however, the trends are not uniformly encouraging. While duodenal ulcer admissions have declined sharply for men, they have risen for women.[5] By 1981, the prevalence of duodenal ulcer in men and women was equal, erasing a long-standing male predominance. The reasons for the changing rates of duodenal ulceration are not known. Changes in individual exposure to ulcerogenic environmental factors have been proposed as an explanation. It is interesting to note, in this regard, that cigarette smoking, a major risk factor for duodenal ulcer, has a pattern similar to duodenal ulcer admission and mortality rates.[6] Cigarette smoking has declined sharply in American men in the past 20 years and only slightly or not at all in women during the same period of time.[7-10] The changes in ulcer incidence cannot be attributed to the widespread use of histamine-2 receptor antagonists; the declining ulcer rates in men antedate the clinical introduction of cimetidine.

Although the clinical use of H_2-receptor antagonists cannot explain changing rates of duodenal ulceration, cimetidine has had a major influence on the treatment of established ulcers. Specifically, the use of cimetidine has had an enormous impact on surgical practice. In both the United States and in Great Britain, already declining operative rates for peptic ulcer, reflecting the generally declining incidence of the disease, were further decreased by the widespread use of powerful H_2-receptor antagonists.[11,12] The notable drop in peptic ulcer operations after cimetidine's debut reflects the virtual elimination of operations performed for intractability. By contrast, operative rates for complicated ulcer disease, perforation or hemorrhage have remained largely unchanged in the cimetidine era.

Two forces may counter the trend of the decreasing use of operative therapy in peptic ulcer disease. First, the long overall decline in the incidence of peptic ulcer disease may be plateauing. As mentioned, while a slow decline in the incidence in men has continued, peptic ulceration in women is

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increasing.[5] Second, the widespread acceptance of parietal cell vagotomy as an effective treatment has increased surgical options. Parietal cell vagotomy is an effective treatment based on sound physiologic principles that combine a low operative morbidity with a general lack of chronic postoperative side effects.

Basic Gastric Physiology

There are three major stimuli of gastric acid production by parietal cells—histamine, acetylcholine from vagal nerves and gastrin.[13] Each of the three major stimuli activate the parietal cell via separate and specific membrane-bound receptors. The occupation of histamine receptors stimulates a membrane-bound adenylate cyclase, which leads to the generation of intracellular adenosine 3′:5′-cyclic phosphate (cyclic AMP) from adenosine triphosphate.[14-16] Cyclic AMP acts as a second messenger to initiate a series of intracellular reactions that include activation of a protein kinase and subsequently a series of enzymatically catalyzed phosphorylation reactions.[17-19] These intracellular events ultimately result in activation of the parietal cell proton pump.[20] Localized on the luminal membrane, the proton pump is a hydrogen-potassium adenosine triphosphatase that is responsible for transporting hydrogen ions from the parietal cell cytoplasm into the gastric lumen in exchange for potassium against a steep electrochemical gradient. Stimulation of the parietal cell by acetylcholine does not increase intracellular cyclic AMP. Occupation of acetylcholine receptors causes an increase in intracellular calcium ions. Increases in intracellular calcium act through a calmodulin-dependent mechanism to stimulate phosphorylation reactions that ultimately result in activation of the parietal cell proton pump. Investigators have recently reported that after gastrin binds to its receptor, the gastrin-receptor complex leads to the generation of inositol-trisphosphate from membrane-associated phospholipids.[21] Inositol-trisphosphate then causes release of intracellular calcium stored within the rough endoplasmic reticulum, and the rise in intracellular calcium precedes activation of phosphokinase and ultimately of the parietal cell proton pump.

The initial cellular events involved in the stimulation of gastric acid production by gastrin, acetycholine and histamine are quite distinct. Nonetheless, each stimulus ultimately activates the parietal cell proton pump. It is not surprising, therefore, that a strong interdependence of secretagogue action exists. The interdependence has very important clinical implications. For example, a blockade of parietal cell histamine receptors by cimetidine inhibits the acid secretory responses to gastrin and acetylcholine in addition to that caused by histamine. Interrupting afferent vagal impulses by a surgical vagotomy or by specific anticholinergic agents reduces parietal cell responsiveness to endogenous stimulants such as gastrin.

Pathophysiology

A number of physiologic abnormalities have been identified in patients with duodenal ulcer disease, but a single, clearly defined defect has not been identified as the cause for peptic ulceration, reflecting the complexity and heterogeneity of the disease process. Investigations of the pathophysiology of duodenal ulcer have focused in three general areas: abnormalities of gastric acid secretion, defects in endocrine control mechanisms and deficits in mucosal resistance to acid (Table 1).

TABLE 1.—*Potential Pathophysiologic Factors in the Development of Duodenal Ulceration*

Increased acid secretory capacity
Enlarged parietal cell mass
Increased basal acid secretion
Prolonged meal secretory response
Abnormal gastric emptying
Defective mucosal defenses

Patients with duodenal ulcer have, on average, an increased basal secretion of acid.[22] The mechanism responsible for the increased basal secretion is not known, but because basal secretion results from background vagal and histamine stimulation, abnormalities in these two mechanisms have been hypothesized. Duodenal ulcer patients also show a larger and more prolonged acid secretory response to a meal than normal persons,[23] suggesting an increased sensitivity to acid secretagogues released by meal stimulation or defects in feedback inhibition of acid secretion.

As a group, patients with duodenal ulcer have an increased secretory capacity for gastric acid. For example, in response to the intravenous administration of histamine, the mean peak acid secretion in duodenal ulcer patients is about 40 mEq of hydrochloric acid per hour, whereas the mean maximum acid output of normal men is around 20 mEq per hour.[24(p 44)] There is considerable overlap between duodenal ulcer patients and normal subjects, however, and most duodenal ulcer patients fall within the range of values of normal persons. The increased maximal acid output noted in patients with duodenal ulcer may, in part, be due to an increased number of parietal cells.[25,26] Duodenal ulcer patients have an average of 1.8 billion parietal cells in their fundic mucosa, about twice the number for normal subjects.

Disturbances in gastric emptying have also been found in some duodunal ulcer patients. Some patients with duodenal ulcer have accelerated emptying of gastric content, particularly liquids, and duodenal acidification fails to slow emptying appropriately.[27] Recently a study of intraduodenal pH before and after a standard meal showed lower mean pH levels and an increased proportion of time during which the intraduodenal pH remained below 4.0.[28] In affected patients, the total acid load to which the duodenal mucosa is exposed after a meal may be several times that of normal subjects.[29]

No striking endocrine abnormalities have been shown in patients with duodenal ulcer. Basal gastrin levels are not elevated in ulcer patients, and antral gastrin content is normal. Patients with duodenal ulcer tend to release more gastrin after a protein meal, and acidification of the antral lumen is less effective in inhibiting gastrin release in affected persons. These defects in gastrin release do not seem to be crucial in the development of duodenal ulcers, however.

There is no good evidence for defects in secretion of the inhibitory peptide, somatostatin, in the development of duodenal ulceration. Administering somatostatin intravenously inhibits gastrin release and suppresses acid output similarly in ulcer patients and in normal subjects.[30] Circulating levels of somatostatin are normal in duodenal ulcer patients. Reduced tissue levels of somatostatin, however, and fewer antral somatostatin-containing cells have been reported in affected persons.[31] The significance of these observations remains to be determined.

Increasing attention has recently been focused on mucosal

defense mechanisms in the pathogenesis of duodenal ulcer. Because many patients with duodenal ulcers secrete acid and pepsin at a nearly normal rate, it is attractive to postulate a defect in mucosal resistance to acid peptic damage. Both in animals and in humans, prostaglandins have been shown to inhibit gastric acid secretion and to accelerate the healing of established duodenal ulcers.[32-34] Gastric mucosal production of prostaglandin E_2 has been decreased in patients with active ulcer disease, and increases in prostanoid synthesis characterize ulcer healing produced by cimetidine.[35] Further investigation is required to define the role of mucosal prostaglandins in the pathogenesis of duodenal ulcer; the subject is an exciting area of current research.

Another presumed mucosal protective mechanism is bicarbonate secretion by the gastric and duodenal mucosa. The amount of bicarbonate secreted by the stomach is minimal compared with acid secretion, but because the bicarbonate is secreted beneath the mucous gel layer, a small amount of bicarbonate produced in this manner is capable of maintaining the pH at the level of the surface mucous cells near neutrality even in the presence of a low luminal pH. It has been postulated that a defective bicarbonate secretion may exist in patients with duodenal ulcer, but Blair and colleagues have concluded from their studies that gastric bicarbonate secretion is normal in patients with duodenal ulcer disease.[36] Potential abnormalities in mucosal bicarbonate secretion have no proven pathogenetic or therapeutic significance at present.

Medical Therapy

H_2-Receptor Antagonists

The clinical introduction of cimetidine in 1977 revolutionized the treatment of peptic ulcer disease. Cimetidine combines an effective inhibition of gastric acid secretion, long-term safety and a low incidence of undesirable side effects. An estimated 25 million people worldwide have received cimetidine therapeutically. The advances of cimetidine have been continued with the introduction of a second H_2-receptor antagonist, ranitidine. In the first three years after its introduction, almost 3 million people worldwide were treated with ranitidine. While this large clinical experience has shown that these agents are generally effective and safe, a clear definition of the constraints of H_2-receptor blockade has also emerged. Every physician treating peptic ulcer disease requires a clear understanding of the power and of the limitations of these drugs.

The effectiveness of H_2-receptor antagonists in the treatment of duodenal ulcer disease has been extensively described. More than 100 publications have reported the results of "open" trials and of controlled comparisons of the use of cimetidine or ranitidine with placebo or with each other. The evidence is unequivocal that both cimetidine and ranitidine are safe and effective agents for the treatment of duodenal ulcer (Table 2).

With either cimetidine or ranitidine, ulcer healing can be shown endoscopically in about 70% of patients by the end of four weeks.[37] By eight weeks, about 85% to 90% of patients will be ulcer-free and asymptomatic. Initial treatment failures, however, representing the combination of ulcer nonhealing and drug therapy discontinuance because of side effects, are relatively common with both agents. The use of ranitidine for 10% to 15% of patients will fail initially mainly due to persistence of ulcers. Early failures with the use of cimetidine range from 20% to 30%. This higher rate reflects the higher incidence of drug-related side effects seen with cimetidine, mainly mental confusion, interference with drug metabolism and antiandrogenic side effects. During ongoing maintenance therapy (usually 150 mg ranitidine or 400 mg cimetidine given nocturnally), ulcer relapse occurs at similar frequencies for both drugs—10% to 25%.

TABLE 2.—*Clinical Results of Using H_2-Receptor Blockage in Duodenal Ulcer Disease**

Results	*Cimetidine, %*	*Ranitidine, %*
Pain relief	75	75
Ulcer healing—4 wk	60 to 80	60 to 75
Ulcer healing—8 wk	85 to 95	85 to 90
Initial treatment failures	20 to 30	10 to 15
Relapse during maintenance therapy	15 to 25	10 to 25

*Numbers represent percent of patients involved.

Cimetidine and ranitidine are palliative, not curative drugs. They do not change the underlying ulcer diathesis. True maintenance therapy implies a life-long commitment to medical therapy. Reulceration after cessation of H_2-receptor antagonist therapy has been reported in at least half of such patients within a year of discontinuing the drug therapy. Criteria to define the failure of medical therapy are in the process of being redefined, and the concept of the "cimetidine-resistant" ulcer is evolving. Two situations of a clear failure of medical therapy are failure of an ulcer to heal despite 12 weeks of full treatment with H_2-receptor blockade, and the recurrence of an ulcer despite maintenance therapy with H_2-receptor antagonists. For the latter group of patients, a full therapy regimen is often restarted to attempt to heal the ulcer. Criteria that indicate when H_2-receptor antagonist therapy has failed and alternative medical or elective surgical treatment should be considered are clearly needed.

Substituted Benzimidazoles

Substituted benzimidazoles represent a new class of drugs capable of specifically suppressing parietal cell acid production.[38-40] Omeprazole is a member of this group. Omeprazole acts as a proton pump blocker, inhibiting the hydrogen-potassium adenosine triphosphatase located in the secretory membrane of the parietal cell.[41] Chemically, the drug is a weak base and accumulates exclusively in the highly acidic environment of the secretory canaliculus. Omeprazole inhibits the proton pump selectively and almost irreversibly; it inhibits all forms of stimulated acid secretion—gastrinergic, cholinergic and histaminergic.[42-44] Nearly total abolition of acid secretion is possible.

Omeprazole accelerates the healing of duodenal ulcers and provides superior symptomatic relief when compared with cimetidine.[45] More than half of patients who received 30 mg of this drug for the treatment of acute ulceration were painfree within a week. At the end of four weeks, complete ulcer healing, documented endoscopically, was reported in 92% of patients. Omeprazole has not yet been approved for use in the United States. When the drug becomes available, it will represent a significant addition to medical therapy for peptic ulceration.

Selective Anticholinergic Drugs

Experimentally, drugs that block muscarinic receptors for acetylcholine are potent suppressors of gastric acid secretion.

Unpleasant clinical side effects, however, such as a dry mouth, blurred vision, urinary retention and dry bronchial secretions, have limited their usefulness in the treatment of duodenal ulceration. Currently available anticholinergic agents in doses tolerable to human subjects decrease meal-stimulated acid secretion by only 30%, about half the effect that can be obtained with the H_2-receptor antagonists.

Pirenzepine is a selective anticholinergic drug currently undergoing clinical assessment.[46] Pirenzepine belongs to a new class of antimuscarinic agents that interact with muscarinic receptor on postganglionic cholinergic neurons of the stomach (M_1 receptors). The drug does not interact with the classic M_2 receptors of the parietal cells, the pupils, the bladder or cardiac muscle. Pirenzepine effectively inhibits vagally stimulated acid secretion while minimizing unpleasant visual, urinary or cardiac side effects.[47] Pirenzepine does not cross the blood-brain barrier; central nervous system side effects have not been reported.

Several studies have shown that pirenzepine used as a single agent accelerates the healing of duodenal ulceration. Perhaps more important, the combination of selective cholinergic and histamine blockade leads to a substantial reduction in acid secretion. This potentiating effect has been shown in human subjects with hypersecretory states such as the Zollinger-Ellison syndrome, as well as in patients with the usual form of duodenal ulceration.[48] Although using a combination of an H_2-receptor antagonist and an antimuscarinic agent is not necessary for most patients with peptic ulceration, those with cimetidine-resistant ulcers or high-volume gastric output may benefit.

Prostaglandin Derivatives

Prostaglandin derivatives have been studied extensively in the past decade because of their ability to confer resistance to gastric mucosal injury by various ulcerogenic agents.[49] This property has been termed "cytoprotection." Prostaglandins have several pharmacologic actions that may be effective in treating duodenal ulceration. Prostaglandins of the E, A and I classes inhibit histamine-stimulated acid production by blocking the generation of intracellular adenosine monophosphate. Prostaglandin analogues have also been shown to stimulate gastric mucus secretion and to increase the secretion of bicarbonate by the gastric and duodenal mucosa.[50,51] The mechanism by which prostaglandins promote the healing of duodenal ulcers remains to be fully elucidated; nevertheless, they do appear to alter the ulcer diathesis.

Several prostaglandin analogues have undergone clinical trials for the treatment of peptic ulceration. Acceptance of the treatment of duodenal ulceration awaits the elimination of unacceptable side effects, particularly diarrhea and the ability to cause uterine hemorrhage and abortion.[52]

Surgical Therapy

General Considerations

The first consideration in selecting operative therapy for duodenal ulcer should be alteration of the ulcer diathesis in a way that results in ulcer healing with an acceptably low chance of ulcer recurrence. A second goal is treatment of coexisting peptic complications, such as perforation or obstruction. The third major goal of operative treatment is patient safety and freedom from chronic postoperative side effects. When recommending operative treatment, surgeons must select the procedure that best combines safety, prevention of recurrent ulceration and prevention of postoperative disability.

For nearly four decades, vagotomy has been the cornerstone of the surgical treatment of peptic ulceration. Currently, two forms of vagotomy are commonly used. Truncal vagotomy involves dividing both major vagal trunks at the level of the esophageal hiatus of the diaphragm. Truncal vagotomy necessarily results in parasympathetic denervation of liver, pancreas and intestine, in addition to the stomach. Parietal cell vagotomy is done by dividing only those fibers innervating the acid-secreting fundus of the stomach. Vagal fibers to the antrum and the other viscera are preserved.

In humans, truncal vagotomy and parietal cell vagotomy both significantly reduce basal and meal-stimulated gastric acid production. Resting basal acid secretion is reduced by about 80% in the early postoperative period following parietal cell vagotomy.[53] The reduction of basal secretion has been observed at all times during the day and is especially significant during the night.[54] Following a properly done vagotomy, basal acid secretion does not increase significantly with long-term observation. Liavåg and Roland reported that basal acid secretion was reduced by 70% one year after the operation and was not significantly increased from that level five years after the operation.[53] Stimulated acid secretion is also significantly and permanently suppressed after a vagotomy. When patients are stimulated by a meal, by pentagastrin or by insulin-induced hypoglycemia, maximal acid responses are decreased by more than 50% relative to preoperative values as late as five years after a vagotomy.[54]

Doing an antral resection with a vagotomy further reduces acid production. Maximal acid output is decreased by almost 85% compared with preoperative values following truncal vagotomy and antrectomy. This additional reduction in acid production is assumed to result from the removal of antral sources of gastrin and from the loss of potentiative interactions between gastrin, acetylcholine and histamine.

Do the alterations in gastric physiology caused by surgical treatment affect the ulcer diathesis positively? Does surgical treatment permanently alter secretory responses so that ulcers heal initially and remain healed? Data from the large surgical literature that has evolved during the past 40 years suggest that the answer to these questions is unequivocally yes. A large prospective comparison of vagotomy plus pyloroplasty with vagotomy and antrectomy reported the failure of surgical therapy (recurrence at any time during a follow-up period of ten years) in 10% of patients who underwent vagotomy and pyloroplasty and only 3% of those who had vagotomy and antrectomy.[55] Similar results have been reported from many surgical centers and are superior to any so far reported for long-term drug therapy. While consistent results have been achieved in many centers for these two operations, a similar claim cannot yet be made for parietal cell vagotomy. In prospective trials, recurrent ulcers have been reported in as few as 7% or as many as 20% of patients.[56-60] High recurrence rates have often been ascribed to a defect in the operative technique—that is, failing to divide all the vagal fibers before they penetrate the gastric wall. A technique that assures division of all vagal branches involves skeletonization of the distal esophagus, and those who have used this technique are now reporting five-year recurrent rates of no greater than 10%. A variation in recurrence rates depends both on the technique used and on the skill of individual surgeons. Although initial experience with parietal cell vagotomy has not

always been accompanied by high recurrence rates, the operation should probably not be done by surgeons who only occasionally do gastric procedures.

In addition to being effective, elective surgical therapy for duodenal ulcer is safe. A prospective study of 344 patients from Minneapolis who underwent either vagotomy and pyloroplasty or vagotomy and antrectomy reported no postoperative deaths over a 20-year period.[55] Many authors have reported no operative mortality associated with parietal cell vagotomy.[56-60] Serious postoperative complications with all of these procedures have been acceptably low (Table 3).

The indications for an operation in patients with duodenal ulcer are intractability, hemorrhage, obstruction and perforation. It is helpful to have information preoperatively on the location of the ulcer, any anatomic deformity produced by chronic inflammation, the level of serum gastrin and, in some cases, the gastric acid secretory rate. These factors often modify general recommendations on the operative approach (Table 4).

Intractability

Peptic ulcer disease is a chronic, often lifelong, affliction with variable activity extending over many years. Most patients respond promptly to nonoperative therapy during periods of disease activity; a fraction of patients, however, are refractory to treatment or have frequent relapses. For patients in whom drug therapy has been unsatisfactory, parietal cell vagotomy has much to recommend it as the operation of choice when ulcer pain is a persistent problem. Parietal cell vagotomy is preferred because of its safety, low rate of postoperative complications and low incidence of untoward sequelae.

As mentioned previously, parietal cell vagotomy differs from other forms of vagotomy in that the hepatic and celiac divisions are not transected and the nerves of Latarjet providing motor innervation on the antrum and pylorus are left intact. The major advantage of parietal cell vagotomy is the relative freedom from unpleasant postoperative sequelae. Dumping is reported in a few patients (0% to 5%).[56-60] Most symptoms are mild and resolve spontaneously; severe and permanent dumping is almost unknown. Postvagotomy diarrhea is rarely a problem following parietal cell vagotomy because biliary, pancreatic and enteric innervation is preserved. Postoperative diarrhea is usually mild and transient, requiring no specific therapy.

Postoperative recurrences, when they do occur, are more easily managed after parietal cell vagotomy than after truncal vagotomy with pyloroplasty or truncal vagotomy with antrectomy. In a detailed literature review, Stabile and Passaro calculated a mortality of 10.8% and a secondary relapse rate of 42.1% for recurrent ulcer after truncal vagotomy and drainage or resection when medical treatment was used.[61] A large majority of these patients required repeat operations. In contrast, Clark and co-workers have reported successful management of recurrence following parietal cell vagotomy without a surgical procedure using H_2-receptor blockage.[62]

TABLE 3.—*Clinical Results of Operative Treatment of Duodenal Ulceration**

Result	Parietal Cell Vagotomy, %	Truncal Vagotomy and Pyloroplasty, %	Truncal Vagotomy and Antrectomy, %
Operative mortality	0	1	2
Ulcer recurrence	10 to 15	10 to 12	1 to 2
Dumping, moderate to severe	0	1	1 to 2
Symptomatic diarrhea, severe	0	2	1 to 2

*Numbers represent percent of patients experiencing complication.

TABLE 4.—*Preferred Operations in Differing Clinical Circumstances*

Indication	Primary Choice	Secondary Choice
Pain	Parietal cell vagotomy	Truncal vagotomy and pyloroplasty; truncal vagotomy and antrectomy
Hemorrhage	Suture ligation with truncal vagotomy and pyloroplasty	Suture ligation with truncal vagotomy and antrectomy
Perforation	Omental patching with parietal cell vagotomy	Truncal vagotomy and pyloroplasty
Obstruction	Truncal vagotomy and antrectomy	Truncal vagotomy and drainage

Hemorrhage

Hemorrhage is currently the principal cause of death associated with duodenal ulcer and in some series has become the most common reason for an operation. While more than 70% of patients with an upper gastrointestinal hemorrhage will stop bleeding spontaneously, early aggressive surgical therapy is sometimes required. Indications for an immediate operation include massive hemorrhage eventuating in shock, prolonged bleeding with a loss of more than six units of blood, recurrent hemorrhage during a course of medical therapy and readmission to hospital for hemorrhage. The endoscopically noted presence of a blood vessel visible within an ulcer crater has been claimed as an additional indication for surgical treatment.[63] Initial reports suggested that a visible vessel predicted recurrent life-threatening hemorrhage and mandated an operation. Additional experience, however, has shown that, while a visible vessel does indicate an increased risk for rebleeding, its presence is not sufficient, by itself, to warrant an operation.[64]

Hemorrhage is a serious complication that must not be minimized. Devitt and associates identified the characteristics of fatal ulcer hemorrhage.[65] Patients who died had a median of five episodes of hemorrhage requiring hospital admission before death. An insufficient volume or rate of transfusion was identified in 88% of these cases, and a delay in operation was noted in 58%. These authors concluded that ulcer patients, especially elderly persons, cannot tolerate repeated or inadequately replaced blood losses. A definitive surgical procedure is better tolerated than repeated episodes of hypovolemia.

Vagotomy with pyloroplasty is the preferred operation for the emergent treatment of bleeding duodenal ulcer. Truncal vagotomy with antrectomy is an accepted alternative procedure in selected circumstances. Farris and Smith have reported a 6% operative mortality in 100 consecutive patients with bleeding duodenal ulcer after vagotomy, pyloroplasty and suture ligation.[66] McGregor and colleagues have reported a mortality of 8% and ulcer recurrence of only 3.1% in such patients.[67]

Truncal vagotomy with antrectomy is very effective in preventing recurrent hemorrhage, and this operation may be considered if a patient is not elderly, not in shock and is able to withstand the additional operative time associated with gas-

tric resection. Polumbo and Sharpe have reported a postoperative rebleeding rate of less than 5% after vagotomy and resection.[68] Surgeons doing a vagotomy with antrectomy accept the known long-term symptoms associated with gastrectomy and the increased morbidity of a prolonged operation in a patient with hemorrhage in exchange for the increased chance of permanent ulcer healing.[69] Vagotomy with antrectomy effectively prevents recurrent hemorrhage.

Obstruction

Gastric outlet obstruction due to duodenal ulcer disease may be either acute or chronic in nature. Acute obstruction occurs as a result of inflammation and edema, and the gastric retention is resolved in most patients with the use of nasogastric suction and cimetidine given intravenously. Repeated episodes of ulceration and healing may lead to progressive scarring and permanent stenosis. Chronic gastric outlet obstruction, the end result of such a process, complicates 10% or less of cases of duodenal ulcer in modern series. Complete obstruction causes volume depletion and hypochloremic alkalosis due to vomiting of gastric secretions containing hydrochloric acid. Long-standing incomplete obstruction leads to weight loss and occasionally cachexia.

All patients presenting with acute or chronic obstruction should initially be treated with medical therapy consisting of gastric decompression and intravenous hydration. Total parenteral nutrition should be instituted early for those with weight loss. The presence of a fixed stenosis can usually be inferred by a positive saline load test after 72 hours of maximal medical therapy.[70] Positivity consists of a gastric residual of 400 ml 30 minutes after instillation of 750 ml of a saline solution into the stomach. Obstruction due to acute inflammation almost always relents by 72 hours with the use of nasogastric suction and cimetidine. Upper gastrointestinal endoscopy is usually done to confirm the mechanical nature of the obstruction, and after this has been done, the only reason for delay in operative therapy is the need for nutritional repletion.

The operation for obstruction should both relieve the ulcer diathesis and treat the gastric obstruction. Truncal vagotomy with antrectomy combines superior efficacy in preventing recurrent ulceration and is recommended as the procedure of choice for obstruction. If extensive duodenal scarring makes gastric resection difficult, truncal vagotomy with gastrojejunostomy is a logical second choice. The extensive duodenal scarring usually present in cases of obstruction often makes a satisfactory pyloroplasty difficult to do.

Using vagotomy and antrectomy, Hoerr and Ward have reported very satisfactory results, with a less than 4% chance of recurrent ulceration.[71] Postoperative gastric atony has been suggested to occur with a high frequency following operations for obstruction that include vagotomy,[72,73] but several authors have used various vagotomy operations and have not reported delayed gastric emptying.[71,74] Vagotomy is an essential element of operations for duodenal ulceration and should not be omitted in this circumstance; preoperative decompression of the stomach for 72 hours usually minimizes problems of gastric atony.

Perforation

Free perforation of a duodenal ulcer is an indication for an emergency operation in all but a few cases. At the time of laparotomy, the major decision is usually whether simple closure of the perforation is adequate or whether a definitive ulcer operation should be added to the closure. The benefits of a definitive operation are obvious: freedom from continued ulcer symptoms and protection from the complications of recurrent ulcer. The disadvantage of a policy of a definitive operation for all patients is that about a third of these patients would not require definitive treatment after patch closure and would be unnecessarily subjected to unpleasant postoperative side effects.[75]

In unselected series, long-term follow-up after simple closure has shown that recurrent ulceration occurs in about 80% of such patients.[76] If definitive treatment is not carried out, 9% of these patients may be expected to reperforate.[77] Greco and Cahow have reported that most patients who require additional therapy after simple closure are men, aged to 40 to 64 years, with a clear history of chronicity for more than three months before perforation.[78] Younger patients without a history suggestive of chronic disease and with no duodenal scarring indicative of previous ulceration may be treated by simple closure with less than a 20% chance of postoperative recurrence.

Before a definitive ulcer operation can be recommended, the following criteria must be satisfied:

- There must be historical or anatomic evidence of chronic ulcer disease.
- The patient must be expected to tolerate the additional operative time necessary for a definitive operation.
- The procedure should have virtually no mortality.
- The procedure should provide excellent protection against recurrent ulceration.
- Undesirable postoperative effects should be minimal.

Boey and co-workers, in a prospective study, identified risk factors for death and complications in patients with free perforation.[79] Serious concurrent medical illness, preoperative shock and long-standing perforations of greater than 48 hours' duration were the features that increased mortality. These authors recommended that a definitive surgical procedure not be done in the presence of any of these factors. In their absence, however, a definitive ulcer operation can be done with an operative risk equivalent to that for simple closure. In patients receiving prompt surgical attention, this mortality risk should now approach zero.[80-82]

Recently, parietal cell vagotomy plus patch closure of the perforation has received a good deal of support as the operation of choice in the treatment of perforation. Jordan has reported a recurrence rate of less than 2% when parietal cell vagotomy is done for acute perforation.[81] These excellent results have been confirmed by Boey and associates in a prospective trial of carefully selected patients.[82] In their report, the results after parietal cell vagotomy were significantly superior when compared with those after closure alone or vagotomy with pyloroplasty. We recommend that an appropriately aggressive operative approach should be used in patients with evidence of chronic ulceration, with parietal cell vagotomy added to omental closure whenever a patient's condition permits.

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Emergent Management of Chemical Burns

THE TREATMENT OF CHEMICAL BURNS that everyone should be aware of is: One, remove all the clothing. This is not a time for modesty. Regardless of the situation, the clothing should come off. Prolonged contact with the chemical in the clothing is going to increase the severity of the injury. We have seen instances in which people have had chemicals soaked in their clothing and because of modesty, or for whatever reason, never had their clothing taken off until they got to an emergency department. So during that entire time, a chemical was penetrating and causing more damage. For the vast majority of injuries, water lavage is the appropriate treatment. There is no time to go out and look for the specific neutralizing agent for that chemical. Moreover, a small water fountain that puts out a gallon of water every hour will not be sufficient. You need a huge lavage. Probably the most common one that people will have in their workplace is an overhead shower. If there is no shower available, there may be a water hose around. A large volume of water is needed and the lavaging needs to be continued for a prolonged period. There are a few exceptions to immediate water lavage. White phosphorus is a material that basically ignites when exposed to water. It should be covered with oil. Sodium metal is in the same category—it needs to be covered with oil, and then the material removed from the skin. Mustard gas should be washed off, preferably with a petroleum of some form—kerosene, gasoline or oil. Lime, when mixed with water, becomes a strong alkali and will cause more damage. Lime should be wiped away, brushed away or blown away, followed by a large-volume water lavage. Most of the lime can be dusted away or blown away. There is some mention in the literature that strong acids should not be lavaged with water. The reason is that very strong acids—sulfuric, hydrochloric or nitric—will release heat when lavaged with water. That is true in small volumes. If you have a large volume of water, however, you immediately wash that away. In the vast majority of the cases, persons with chemical injuries are not going to die of their burns at the scene—unless they have also inhaled some materials or unless they have some other trauma. They are not going to die in the first 20 minutes—they are going to die in the first week. And so it is much more important to get the chemical washed off and a minimum of a 20-minute lavage done at the scene.

—LYNN D. SOLEM, MD

Extracted from *Audio-Digest Emergency Medicine*, Vol. 4, No. 10, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Chemotherapy for Bacterial Infections of the Central Nervous System

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Over the past six years, many new agents have become available for the treatment of bacterial central nervous system (CNS) infections. Certain principles guide the use of these agents for CNS infections: first, an antimicrobial agent must be able to penetrate the CNS to be effective; second, the CNS is a "relatively immunoincompetent site" so that an antimicrobial must achieve levels within the CNS capable of killing the offending bacterium. The lack of efficacy of chloramphenicol for meningitis due to gram-negative aerobes is probably due to its failure to achieve such killing levels, whereas the success of the newer cephalosporins, such as cefotaxime and ceftriaxone, is due to their very high killing activity against these organisms. Penicillin remains the first choice for pneumococcal and meningococcal meningitis. Ampicillin plus chloramphenicol is still recommended as initial therapy for meningitis due to Hemophilus influenzae. *The newer cephalosporins are now the first choice for the treatment of meningitis due to many gram-negative bacilli. Trimethoprim-sulfamethoxazole may also be useful in some of these infections and those due to* Listeria monocytogenes. *In the treatment of severe CNS infections, a team approach is advised to ensure optimal therapy.*

(Ampel NM, Labadie EL: Chemotherapy for bacterial infections of the central nervous system. West J Med 1987 Sep; 147:309-313)

Since one of us (E.L.L.) reviewed the topic of chemotherapy for central nervous system (CNS) infections six years ago,[1] there have been significant developments. This has been due in part to the introduction of a variety of new antimicrobial agents, including second- and third-generation cephalosporins, which are being used with increasing frequency. In this article we review the rationale and current recommendations for the treatment of bacterial infections of the CNS. Given the breadth of the topic, only the most common infections will be covered.

Principles of Chemotherapy

Certain principles guide the use of antimicrobial agents for CNS infections. The first is that an antimicrobial agent must be able to penetrate into the CNS to be effective. Norrby has indicated that there are actually two distinct barriers curtailing drug entry into the CNS.[2,3] The first has to do with the ability of a drug to enter the cerebrospinal fluid (CSF) from the blood and is referred to as the blood-CSF barrier. The second is a barrier to the entry of a drug from the blood into brain parenchyma itself. It appears that the blood-brain barrier may be less permeable to drug entry compared with the blood-CSF barrier.[2,3]

Several characteristics of a drug determine its ability to enter the CSF. The two most important of these are the degree of ionization at physiologic pH and the lipid solubility of the drug.[2] Only the unionized portion of a drug will enter the CSF. Further, the more lipid soluble a drug is, the more likely it is to enter. Drugs such as chloramphenicol, which exist primarily in unionized form and are highly lipid soluble, enter the CSF readily. On the other hand, penicillins, which are very ionized at physiologic pH and are not lipid soluble, enter at very low concentrations. Additional drug characteristics that play a role in inhibiting penetration into the CSF are a large and complex molecular size and a high degree of protein binding in serum.[2]

Other factors also determine the effective concentration of an antimicrobial in the CSF. Inflammation of the meninges due to bacterial infection increases the permeability of the blood-CSF barrier and allows drugs to enter much more readily.[2] For many β-lactam antibiotics, efficacy in patients with bacterial meningitis is dependent on this altered permeability.[4] While most drugs are removed from the CSF by bulk flow, penicillins are actively transported out of the subarachnoid space through the choroid plexus. Such transport is inhibited by meningeal inflammation and the use of probenecid, resulting in higher concentrations of penicillins in the CSF.[4] In vivo metabolic alterations of an antimicrobial agent may also alter its efficacy in the CSF. Nolan and Ulmer[5] found that cephalothin was metabolized to desacetylcephalothin by the choroid plexus. This resulted in higher concentrations of this less active cephalothin metabolite in the CSF, perhaps explaining the poor results of cephalothin in treating bacterial meningitis.

Another therapeutic principle relates to the fact that the central nervous compartment is a "relatively immunoincompetent site."[6] Simberkoff and co-workers reverified the well-known fact that CSF contains nearly undetectable amounts of immunoglobulin and complement and so lacks the ability to kill a large variety of microorganisms.[7] In addition,

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ABBREVIATIONS USED IN TEXT
CNS = central nervous system
CSF = cerebrospinal fluid
TMP/SMX = trimethoprim-sulfamethoxazole

normal CSF contains very few leukocytes, and once leukocytes do enter the CSF, their phagocytic activity may be inefficient because of the scarcity of immunoglobulins and complement. Therefore, for optimal therapy, an antimicrobial agent should achieve levels in the CSF many times above the minimum bactericidal concentration of the antimicrobial as measured in vitro. This concept is affirmed by the experimental work of Scheld and Sande where a favorable outcome was found to be closely associated with achieving much higher antimicrobial levels in the CSF above the minimal bactericidal concentration in vitro.[8]

A clinical outcome depends not only on reaching high antimicrobial concentrations in the CSF, but also on the ability of an antibiotic to kill the offending organism. For instance, Rahal and Simberkoff have shown that chloramphenicol, which is bactericidal against *Streptococcus pneumoniae, Hemophilus influenzae* and *Neisseria meningitidis,* yields successful clinical outcomes.[9] On the other hand, chloramphenicol was found to be only bacteriostatic at levels achievable in the CSF against most gram-negative bacilli. The outcome of patients given chloramphenicol for gram-negative bacillary meningitis has been very disappointing.[10]

Some of the newer second- and third-generation cephalosporins have combined the ability to penetrate into the CSF at moderate levels with notable bactericidal activity against many meningeal pathogens.[11,12] Cefuroxime,[13] cefotaxime[14,15] and ceftriaxone[16-18] have been most extensively studied and appear to be highly effective. Although moxalactam has also been used successfully for the treatment of meningitis due to gram-negative bacilli,[19-21] it has poor activity against many gram-positive bacteria[22,23] and its use has been associated with a bleeding diathesis.[24,25] Because of these problems, it probably will no longer be used for CNS infections.

The best method for delivering antibiotic therapy to the CSF has been debated.[4] Intravenous therapy given as an intermittent bolus infusion appears to achieve the highest levels of antimicrobial in the CSF.[26,27] The specific indications for the direct instillation of antimicrobials into the CSF will be discussed later. In general, the intrathecal use of antimicrobials requires distinct precautions. It should be reserved for those cases in which therapy requires higher CNS levels of an antimicrobial agent than can be achieved with parenteral treatment—such as with the use of vancomycin hydrochloride or gentamicin sulfate. Injection should be done by those experienced in the procedure, using preservative-free antimicrobial solutions in all instances.

Recommended Antimicrobial Therapy for Specific Infections

High-dose penicillin G remains the antibiotic of choice for meningitis due to *S pneumoniae* and meningococcal meningitis (Table 1). Pneumococcal strains, however, that are relatively resistant to penicillin (minimum inhibitory concentration between 0.1 and 1.0 μg per ml) are being reported with increasing frequency in the United States, and therapeutic failures with the use of penicillin in pneumococcal meningitis have been recorded.[28] In these cases, and in those with known penicillin allergy, chloramphenicol is currently recommended. Chloramphenicol is the second choice for treating meningococcal meningitis as well. Cefuroxime,[13] cefotaxime[14,15] and ceftriaxone[16-18] also appear to be effective therapy for pneumococcal meningitis and may be alternatives for the treatment of meningitis due to these relatively resistant strains.

Therapy for *H influenzae* meningitis has become more cumbersome due to the emergence of β-lactamase-producing strains. Currently, the accepted practice is to begin treatment with a combination of ampicillin and chloramphenicol. Once the sensitivities of the organism are known, the use of one of the antibiotics is stopped. The emergence of chloramphenicol-resistant strains of *H influenzae* may alter this therapeutic approach in the future. Single-drug therapy with either cefuroxime, cefotaxime or ceftriaxone for *H influenzae* meningitis is a newer alternative recommended by some.[28]

Penicillin G or ampicillin is the recommended drug for treating patients with meningitis due to the group B streptococcus, a common cause of neonatal meningitis. Swingle and colleagues, however, have shown in vitro that low concentrations of gentamicin, achievable in the CSF with standard dosing, significantly accelerate the killing of many strains of group B streptococci by penicillin or ampicillin.[29] Because some strains of these organisms have been found to be tolerant to penicillin, a combination regimen with penicillin and gentamicin may become more clinically relevant treatment.[30,31] New cephalosporins, such as cefotaxime and ceftriaxone, are active against group B streptococci, but they are no more potent than giving penicillin alone[32,33] and probably offer no therapeutic advantage to its use.

Other streptococci can be treated with either penicillin G or ampicillin with the exception of the group D enterococcus. This organism is relatively resistant to penicillin. Bayer and associates have recommended intravenously given ampicillin as the initial therapy.[34] If there is no response, a parenterally administered aminoglycoside should be added. If the response is still poor, then the aminoglycoside may be given intrathecally. Because this "staged" approach may be unduly prolonged, we recommend beginning with a combination of ampicillin and gentamicin given parenterally, followed without delay by gentamicin given intrathecally if there is no response. Intrathecally administered vancomycin has also been used successfully to treat enterococcal meningitis in penicillin-allergic patients.[35,36] Fortunately, enterococcal meningitis is rare.

The greatest impact of the new cephalosporins has been in the treatment of meningitis due to aerobic gram-negative bacilli. Before the introduction of these agents, therapy was difficult and often involved giving antibiotics, such as aminoglycosides, intrathecally.[37] Although some cases of gram-negative bacillary meningitis in adults have been cured with intraventricular administration of gentamicin,[38] intrathecal therapy with gentamicin has not been shown to be more effective than parenteral therapy in neonates,[39,40] who lack the tight blood-CSF barrier of adults. Several third-generation cephalosporins have been effective in treating gram-negative bacillary meningitis when given as single agents parenterally, including moxalactam,[20,21] cefotaxime[15,41] and ceftriaxone.[12,28,42] Currently, third-generation cephalosporins are the agents of choice for treating gram-negative bacillary meningitis if the organism is susceptible. Recent experience sug-

gests that trimethoprim-sulfamethoxazole (TMP/SMX) given intravenously may also be beneficial for the treatment of meningitis due to susceptible organisms,[43,44] including *Enterobacter, Serratia* and *Proteus* species.

Therapy for meningitis due to *Pseudomonas aeruginosa* can be more difficult. The new cephalosporins mentioned earlier and TMP/SMX have little activity against this organism. Some recent success has been noted, however, with ceftazidime,[12,45] a third-generation cephalosporin with antipseudomonal properties. Intrathecal administration of gentamicin may be required in recalcitrant cases of seriously ill patients.

Parenterally given ampicillin plus gentamicin is the regimen of choice for the treatment of meningitis due to *Listeria monocytogenes*. In vitro studies and studies in animals suggest that ampicillin is more active than penicillin against this organism.[46,47] Although chloramphenicol was once considered as an alternative, recent experience suggests it is not effective.[10,48] Several cases of *Listeria* meningitis have also been successfully treated with TMP/SMX.[44,49]

Staphylococcal meningitis is often due to the contiguous spread of infection from neurosurgical or other head wounds or from cranial osteomyelitis. High-dose nafcillin given intravenously is the preferred therapy. An increasingly common cause of staphylococcal CNS infection is due to infected CSF shunts or intraventricular reservoirs. In most instances, successful therapy requires removal of the shunt or reservoir plus parenteral or even intrathecal antimicrobial

TABLE 1.—*Antimicrobial Therapy for Central Nervous System Bacterial Infections—Specific Recommendations**

Infecting Organism	*1st Choice†*	*2nd Choice†*	*Comments*
Streptococcus pneumoniae	Penicillin G: A, 24 million units; C, 250,000 units/kg; D, 2 to 4 h	Chloramphenicol: A, 4 grams; C, 100 mg/kg; D, 6 h	Rare strains are relatively resistant to penicillin
Neisseria meningitidis	Penicillin G	Chloramphenicol	Serum concentrations should be monitored if chloramphenicol is used
Hemophilus influenzae	Ampicillin: A, 12 grams; C, 200 mg/kg; D, 4 to 6 h; *plus* chloramphenicol	Cefuroxime: A, 9 grams; C, 200 to 240 mg/kg; D, 6 to 8 h; *or* cefotaxime: A, 12 grams; C, 200 mg/kg; D, 6 h; *or* ceftriaxone: A, 4 grams; C, 100 mg/kg; D, 12 h	Some authors recommend cefuroxime or 3rd-generation cephalosporins as the first choice for therapy
Streptococci			
Group D enterococcus	Ampicillin	Vancomycin hydrochloride: A, 4 grams; C, 40 to 60 mg/kg; D, 6 to 12 h	Parenteral or intrathecal administration of gentamicin sulfate may be needed in severe cases‡; penetration of vancomycin into CSF is erratic and often poor
Other streptococci including group B	Penicillin G *or* ampicillin	. . .	Adding gentamicin given parenterally to penicillin or ampicillin regimen is recommended for tolerant strains
Aerobic gram-negative bacilli (nonpseudomonal)	Cefotaxime *or* ceftriaxone	TMP/SMX§: A, 10 to 20 mg/kg (TMP); C, 10 to 12 mg/kg (TMP); D, 6 to 8 h	Specific therapy should be tailored to the antimicrobial sensitivities of the infecting organism; at least 3 weeks of therapy are recommended; intrathecally given aminoglycosides may be needed in some cases‡
Pseudomonas aeruginosa	Ceftazidime: A, 6 grams; C, 150 mg/kg; D, 8 h; *plus* gentamicin, *or plus* tobramycin: A, 3 to 5 mg/kg; C, 5 to 7.5 mg/kg; D, 8 h	Ticarcillin: A, 18 to 24 grams; C, 300 mg/kg; D, 4 h; *plus* gentamicin, *or plus* tobramycin	See above note; adequate therapy for pseudomonal meningitis is not established; 2 parenteral drugs are strongly recommended and intrathecal aminoglycoside treatment is often necessary‡
Listeria monocytogenes	Ampicillin *plus* gentamicin	TMP/SMX	The use of 3rd-generation cephalosporins and chloramphenicol is not recommended
Staphylococcus, methicillin-sensitive‖	Nafcillin: A, 12 grams; B, 200 mg/kg; C, 4 h	. . .	Infected shunts or reservoirs should be removed and antibiotic therapy continued until after new insertion
Staphylococcus, methicillin-resistant	Vancomycin	. . .	See above note; intrathecal administration of vancomycin may be required¶
Brain abscess, pyogenic	Penicillin *plus* chloramphenicol, *or plus* metronidazole: A, 2 grams; C, 30 mg/kg; D, 6 h	Cefotaxime *plus* chloramphenicol, *or plus* metronidazole	Surgical drainage is usually necessary; for empiric therapy, penicillin should be used for frontal and cefotaxime for temporal lobe abscesses; therapy is prolonged (weeks to months)
Nocardia species	Sulfisoxazole: A, 8 grams; C, 100 mg/kg; D, 6 to 8 h	TMP/SMX	Peak serum concentrations of 12 to 15 mg/dl are recommended; therapy is prolonged (weeks to months)

TMP/SMX=trimethoprim-sulfamethoxazole

*Unless otherwise specified, the recommended total time of therapy is 10 to 14 days.

†A=total daily intravenous dosage for an adult; C=total daily intravenous dosage for a child older than 4 wk; D=suggested dosing interval. Normal renal and hepatic function is assumed in all instances. Dosages and intervals are not repeated in the table if they are unchanged for subsequent organisms.

‡Intrathecal gentamicin and tobramycin can be given up to 5 mg/day in adults and 1-2 mg/day in infants. Preservative-free solutions should be used

§TMP/SMX is available parenterally as a suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole per 5 ml.

‖If the *Staphylococcus* is sensitive to penicillin, penicillin is the drug of choice.

¶The dosage for intrathecal vancomycin is 1-20 mg daily. Preservative-free solutions should be used.

therapy.[50] Many of these infections are due to *Staphylococcus epidermidis* resistant to penicillinase-stable penicillins, such as nafcillin. In such cases, some authors have reported success with the intravenous use of vancomycin.[51,52] Good results are not universal, however, and CSF concentrations of vancomycin after intravenous administration are erratic.[51] Several cases of shunt or reservoir infection due to *S epidermidis* have been successfully treated by injecting vancomycin directly into the ventricles through the infected device.[53,54]

Pyogenic brain abscess has been most commonly treated by a combination of surgical excision and adjunctive antibiotics. With close monitoring through the use of cranial computed tomographic scans, however, there are now several instances of successful treatment using antibiotics alone.[55] Parenteral administration of penicillin plus chloramphenicol has been used traditionally to treat brain abscesses, particularly those located in the frontal lobe, which are often of paranasal and frontal sinus origin.[56] Abscesses arising from an otogenic source usually spread to the temporal lobe or cerebellum and often contain a mixed flora including aerobic gram-negative bacilli and obligate anaerobes.[57,58] In such cases, a third-generation cephalosporin plus metronidazole or chloramphenicol given intravenously is an appropriate empiric regimen. If the abscess is drained, antibiotic therapy is then altered depending on the specific organisms found.

Nocardia species may cause multilocular brain abscesses, particularly in patients with underlying defects of cellular immunity, as occurs with lymphoreticular malignant disorders, long-term corticosteroid use and other immunosuppressants after organ transplantation. Traditional therapy has been neurosurgical drainage followed by administration of sulfisoxazole at dosages of from 6 to 10 grams per day with peak serum concentrations of 12 to 15 mg per dl.[59] Recent evidence indicates that TMP/SMX is also effective.[60,61] Several other antimicrobials are generally active against *Nocardia* species in vitro, including cefotaxime.[62] The use of third-generation cephalosporins in the treatment of nocardial brain abscesses is not yet clinically established, however. Combinations of sulfonamides with other drugs active against *Nocardia* species, including cefotaxime, have also been used. As with other pyogenic brain abscesses, there are instances where antimicrobial therapy without drainage has been successful.[63]

Corticosteroids in the Treatment of CNS Infections

The adjunctive use of corticosteroids in the treatment of bacterial meningitis and brain abscess remains undefined. There are several possible benefits to their use, including lowering of intracranial brain pressure, decreasing cerebral edema and diminishing arteritis and pyogenic thrombophlebitis.[1,64-69] Studies using animals indicate that corticosteroids do have some beneficial effect in cases of meningitis. Scheld and co-workers have shown that CSF outflow resistance became significantly diminished in rabbits with experimental meningitis, ameliorating increased intracranial pressure, when methylprednisolone sodium succinate was administered, whereas antibiotic treatment alone did not alter CSF outflow resistance.[65] Tauber and associates used a similar model to show that dexamethasone, but not methylprednisolone, reversed brain edema, decreased CSF lactate levels and diminished CSF pressure significantly.[66] Because of their anti-inflammatory effect, corticosteroids may decrease the entry of some antibiotics into the CSF, but it remains unclear if this diminution in penetration is significant.[64,67] Indirect clinical evidence suggests that in seriously ill patients dexamethasone at high doses may be life-saving. Randomly selected patients with typhoid fever in whom obtundation and stupor developed had a greatly improved survival rate when given dexamethasone in addition to chloramphenicol.[68] Although numerous individual case reports describe the beneficial effects of corticosteroids in patients with brain abscess—congruent with our own experience—no formal scientific study has reliably answered questions about their indications and limitations.[69-72] In addition, the theoretical concern that corticosteroids may decrease a host's immune response still remains. At this time, therefore, the use of corticosteroids cannot be recommended for the routine treatment of bacterial meningitis or brain abscess. Their use should be reserved for seriously ill patients and guided by an experienced neurologist or neurosurgeon.

Special Considerations

The Team Approach

With the advent of more powerful antibiotics, some physicians may be inclined to treat CNS infections initially without the advice of consultants. We suggest that early consultation with infectious disease and neurologic specialists is always preferable. Patients with fulminant presentations, rapidly changing levels of consciousness, multifocal neurologic signs or those in whom there has been an undue delay in diagnosis or failure of initial medical therapy will urgently require intervention by these other specialists.[69-71]

The approach followed by neurologists and neurosurgeons in these cases is to immediately halt progression of the infection and minimize neurologic impairment by reducing intracranial pressure. For these purposes they prefer at least one parenteral antibiotic with the unquestionable ability to enter the CSF-CNS compartment. If the infecting organism requires an antimicrobial agent with poor penetration—such as gentamicin for *P aeruginosa*—they are likely to initiate early intrathecal administration concurrently with parenteral therapy. Whenever intracranial pressure is deemed uncontrolled, fluid restriction to less than 1,000 ml per day and the use of furosemide and acetazolamide may be recommended to decrease CNS edema and CSF overproduction. If acute hydrocephalus occurs despite dehydration, neurologic and neurosurgical consultants may suggest a temporary ventriculostomy for five to six days and may even resort to the use of dexamethasone if there are signs that neurologic impairment has worsened.

Such treatment tenets may disconcert general physicians experienced in the management of infections of other organs, where fluid and electrolyte requirements during fever are commensurately higher but organ swelling clinically irrelevant. The opposite holds true for CNS infections; seldom do patients die of shock or systemic dissemination, whereas brain swelling is a critical factor that demands early decisive measures to forestall its progression.

The purpose of this final section has been to outline possible sources of confusing divergence among consultants of different specialties during patient management. The optimal care of patients with severe bacterial infections of the CNS often requires a cohesive team approach.

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Asthma Mortality

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Asthma is an extremely common condition, but because it so often presents as a mild although troublesome illness, its lethal potential may be underappreciated. Recent evidence of a possible worldwide increase in asthma mortality has renewed interest in defining those most at risk of fatal attacks and in the steps that might be taken to protect them. Homer Boushey, MD, Associate Professor of Medicine at the University of California, San Francisco (UCSF), will discuss an illustrative case and will review this important subject.*

JONI NICHOLS, MD:† The patient, a 70-year-old woman, was admitted for acute exacerbation of asthma. She had been free of pulmonary complaints until six years ago when, coincident with her move to San Francisco, she began to have recurrent episodes of chest tightness, wheezing and shortness of breath. She was diagnosed as having asthma and was treated with a regimen of theophylline and a metaproterenol sulfate inhaler. For the past four years she has also required between 5 and 30 mg of prednisone per day. Pulmonary function tests two years ago showed a forced expiratory volume in one second (FEV_1) of 1.0 liter and a forced vital capacity of 2.8 liters. The patient had been doing fairly well over the six months before admission until she contracted an upper respiratory tract infection with nasal congestion, general malaise and a nonproductive cough. Over the next two days wheezing and increasing shortness of breath developed. Her symptoms did not resolve despite five treatments with nebulized metaproterenol, and she came to the emergency department for further therapy. She had never previously required admission to hospital for asthma. She said she did not have fevers or chills but did complain of mild anterior pleuritic chest pain with cough. She has a 35-pack-year history of smoking but quit five years ago.

Her medical history is significant for coronary artery disease with a two-vessel bypass graft in 1979 and a hysterectomy in 1976. She also had had tuberculosis for which she was treated from 1970 to 1973.

On admission her medications included prednisone, 10 mg alternating with 5 mg per day, theophylline, metaproterenol aerosol by nebulizer, which she used "as needed" at home and also albuterol and cromolyn sodium inhalers, hydrochlorothiazide and triamterene (Dyazide) and estrogen supplements.

On arrival in the emergency department the patient was acutely dyspneic, using her accessory muscles of respiration. Her blood pressure was 176/50 mm of mercury with a paradoxical pulse of 30 mm of mercury, the pulse rate was 104 per minute and regular and she was afebrile. Examination of her head, eyes, ears, nose and throat showed only a dull right tympanic membrane; her pharynx was clear, and she had no evidence of thrush. Her neck was supple; there was no lymphadenopathy. On chest examination her lungs were found to be moving small volumes of air and she had diffuse expiratory and inspiratory wheezes and a prolonged expiratory phase. A cardiovascular examination showed no jugular venous distention. Her heart tones were normal; there was a soft systolic ejection murmur at the left sternal border. She had no peripheral edema or clubbing. The rest of the examination elicited no abnormalities.

On laboratory studies, a leukocyte count was 12,500 per μl with a hematocrit of 42.6%, and a blood theophylline concentration was 10 μg per ml. Serum electrolyte values were normal. A chest x-ray film showed flattening of the diaphragm, an increased anteroposterior diameter and some peribronchial cuffing; there were no infiltrates and the heart size was normal. Her electrocardiogram was also normal. Initial blood gas determinations with the patient breathing two liters of oxygen by nasal prongs showed a pH of 7.38, a partial carbon dioxide pressure (P_{CO_2}) of 43 mm of mercury and a partial oxygen pressure (P_{O_2}) of 61 mm of mercury. She was unable to do spirometry.

She received several nebulized metaproterenol treatments in the emergency department, and her symptoms abated for 15 to 30 minutes following each treatment, but recurred thereafter. Repeat blood gas values showed no improvement. The patient was admitted to the medical service and was treated with intravenous administration of methylprednisolone sodium succinate and theophylline and hourly inhalations of nebulized metaproterenol. Despite this treatment, her condition deteriorated and a repeat blood gas determination with the patient breathing oxygen by nasal prongs at six liters per minute showed a pH of 7.20, P_{CO_2} 60 mm of mercury and P_{O_2} 100 mm of mercury. She was then transferred to the intensive care unit, an endotracheal tube was introduced and she was mechanically ventilated. Over the next 48 hours her bronchospasm lessened dramatically and the endotracheal tube was removed without difficulty. A regimen of theophylline, inhaled metaproterenol and tapering doses of corticosteroids was continued, and she was discharged after seven days in hospital.

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(Boushey HA, Nichols J: Asthma mortality [Medical Staff Conference]. West J Med 1987 Sep; 147:314-320)

ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in one second
P_{CO_2} = partial pressure of carbon dioxide
P_{O_2} = partial pressure of oxygen
UCSF = University of California, San Francisco

HOMER A. BOUSHEY, MD:* This patient's history may seem inappropriate for a discussion of asthma mortality, for she survived the attack and continues to attend our clinic regularly. It is, fortunately, increasingly difficult to find hospital records of patients who would be appropriate, for death from asthma is now uncommon in patients who make it to a well-equipped and alert emergency department. This does not mean, however, that dying of asthma is now unknown. In fact, evidence of a worldwide increase in asthma mortality prompted the Food and Drug Administration, the National Institutes of Health, the World Health Organization and the American Thoracic Society to cosponsor a task force on asthma mortality. The task force first met in Bethesda, Maryland, last November, and its purposes were to review the evidence suggesting an increase in asthma mortality, to describe the characteristics of patients most at risk of dying of the disease and to identify the likely causes of death and the steps we might take to prevent them. In this review I will present some of the task force's preliminary conclusions and my own thoughts on the causes of what some are already calling an "epidemic" of asthma deaths.

Historical Perspective

Asthma is a very old disease. The word asthma itself is derived from the ancient Greek for "panting." It was early recognized as potentially fatal. In the second century AD Aretaeus of Cappadocia described the symptoms of an asthmatic attack and remarked that they could progress to death by suffocation. Moses Maimonides' 12th century treatise on asthma states that death from asthma can occur "should the rules of management go unheeded and one's desires and habits be followed indiscriminately." Perhaps the first postmortem study of asthma was described to the Royal Society by Watson in 1764. He was particularly impressed with the enormous overdistention of the lungs and with his inability to decompress them by external pressure. Despite Henry Salter's careful description of age, progressive or frequent symptoms and persistent sputum as unfavorable prognostic features that increase the risk of death, the 19th century brought a curious change in attitudes toward asthma. Laennec, the discoverer of the stethoscope and an experienced lung physician, believed that asthma conferred a prospect for long life and freedom from other diseases. Oliver Wendell Holmes called asthma "a slight ailment that prolongs longevity." Even the great William Osler told his colleagues, "the asthmatic patient pants into old age." This attitude extended to the lay world. Proust typifies our image of an asthmatic person as a neurotic, hypochondriacal shut-in, and in *The Plague*, Camus's physician-narrator speculates that an asthmatic patient's condition somehow confers protection against the epidemic. These myths about asthma—that it is primarily a psychosomatic disorder and that it is not life-threatening—still cause mischief in our society. Many parents of asthmatic children carry an inappropriate burden of guilt, believing that their failure in parenting is somehow responsible for the disease. Other parents of asthmatic children, and many adults with asthma, believe that strength of character can overcome asthmatic attacks. These attitudes can lead to tragedy. Surveys have repeatedly shown that suboptimal maintenance therapy, delays in seeking medical attention for acute symptoms and inadequate treatment of acute attacks are common features of most asthmatic deaths.

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Asthma's Lethality

The demographics of asthma suggest some reason for complacency about the disease. Asthma is a common condition, affecting between 3% and 8% of the United States population, but it causes only 2,000 to 3,000 deaths each year. In the course of their careers, most physicians are thus likely to see many patients with the disease but very few patients die of it, especially because most deaths now occur out of hospital. The renewed recognition of asthma as a potentially lethal disorder probably dates from 1922 when Huber and Koessler described the pathologic features of the lungs in 21 people dying of asthma.[1] Their findings have been confirmed in many subsequent studies and are also found, although to a lesser degree, in patients with asthma who die of accidents while in symptomatic remission. The pathologic features include gross hyperinflation of the lungs due to airway obstruction from contraction of hypertrophied, hyperplastic smooth muscle and intraluminal inspissation of mucus. The airway mucosa is infiltrated by inflammatory cells. Many eosinophils are typically found, but an increased number of polymorphonuclear neutrophils is often seen as well. Epithelial desquamation is a common feature of asthma, and the mucous plugs in the airways contain both inflammatory cells and epithelial cells. The airway submucosal glands are enlarged, and there is both hypertrophy and hyperplasia of secretory cells.

These pathologic findings have clear implications for therapy. The finding of hypertrophied, contracted airway smooth muscle certainly suggests that drugs aimed at relaxing airway smooth muscle should be beneficial. This has indeed been the focus of therapy, perhaps excessively so, in this century. The evidence of a disturbance in mucus secretion is harder to act on, for we know little about the regulation of mucus secretion in healthy people, let alone in those with disease.

Inflammatory cell infiltration has only lately become appreciated as an important feature of asthma, and recent work suggests that it may be related to the pronounced increase in the reactivity of airway smooth muscle that characterizes asthma.[2] Anti-inflammatory agents, most notably corticosteroids and sodium cromolyn, have become subjects of intense interest in asthma therapy.

British Asthma Epidemic

The reawakening of the medical profession to asthma's potential for causing death took a much bigger event than Huber and Koessler's report on the pathologic features of asthmatic deaths; it occurred with the sudden and dramatic increase in asthmatic deaths in the United Kingdom in the mid-1960s. This epidemic had a tremendous impact because it disproportionately affected children and young adults. The death rate from asthma increased threefold in adults younger than 34 years and sevenfold in children aged 10 to 14 years, becoming briefly the fourth most common cause of death in this age group. This occurred in the absence of an identifiable increase in the prevalence of asthma or of any change in

diagnostic criteria. The causes were investigated by Frank Speizer, an American physician then in London on sabbatical leave. He reviewed all deaths from asthma in the 5- to 34-year-old age group over a six-month period and was impressed that many of the deaths occurred unexpectedly and that 85% of those who died had used pressurized adrenergic aerosols in the few hours before their death.[3,4] Speizer was also impressed that the use of these agents had often been excessive and described several dramatic cases of aerosol abuse. One was of a teenaged boy seen running down a soccer field with a pressurized cannister in hand, using it several times before dying suddenly and unexpectedly at the end of the playing field.

Concentrated Aerosol Hypothesis

The idea that pressurized cannisters of sympathomimetic drugs were responsible for the increase in the death rate was intriguing, especially because a high-dose preparation of isoproterenol (isoproterenol forte) was then being marketed in the United Kingdom. This preparation delivered 400 μg of isoproterenol per puff, as opposed to the 80 to 100 μg distributed by ordinary cannisters. The theory that arrhythmias induced by isoproterenol could be responsible for the increase in death rates was made more convincing by the increase in asthma mortality in Australia and New Zealand where the high-dose preparation was also sold. The death rate did not increase in the United States or Canada, where the preparation was not marketed.[5]

This idea, which came to be known as the "concentrated aerosol hypothesis," received sensational coverage in the lay press. The United Kingdom Committee on Safety and Drugs published a warning to all physicians, restricted sales of cannisters of adrenergic agents and encouraged the development of β_2-selective agents. The subsequent fall in both asthma mortality and isoproterenol sales seemed to prove the hypothesis.

"Aeroallergen" Theory

The concentrated aerosol hypothesis, however, is not supported by all the evidence. First, while studies using animals show that aerosolized bronchodilators can indeed cause cardiac arrhythmias and that these arrhythmias are potentiated by the propellant gases used in aerosol cannisters, the blood concentrations required for these effects are vastly greater than the blood concentrations found in people even when they use doses far in excess of those prescribed. Second, myocardial contraction bands, once thought of as markers of catecholamine excess, have been found in postmortem studies of the hearts of patients dying of asthmatic attacks that had not been treated with sympathomimetic drugs. Finally, epidemiologic studies in Japan, Australia and the Scandinavian countries do not support the theory. Gandevia, an Australian epidemiologist, analyzed deaths from asthma and the sale of aerosolized adrenergic drugs from 1960 to 1970.[6] He found an increase in mortality over the same years as in the United Kingdom, but the fall in mortality was neither preceded nor accompanied by a fall in the sale of isoproterenol. Further, there was no correlation between the death rate from asthma and the sale of isoproterenol in different regions in Australia. Of Speizer's observation that most asthmatic patients die with a pressurized cannister in their hands, Gandevia wrote, "This finding is perhaps more impressive to the epidemiologist than to the clinician. For the clinician would expect patients to die having dosed themselves with a readily available, popular, and usually effective remedy." An alternate theory has been put forth by Jenkins and colleagues in Wales,[7] who reported that the levels of aeroallergens were particularly high in Cardiff in the mid-1960s, the years of the epidemic, and that asthma deaths and the levels of aeroallergens correlated well over a 17-year period of observation. This theory, that the epidemic of asthma deaths was due to an increase in aeroallergens, is congruent with the observation that deaths were most common in young people, for extrinsic, allergic asthma is more common in the young. It is also congruent with the theory that extreme bronchial hyperreactivity is a risk factor for dying of asthma, for in people with allergic asthma, bronchial reactivity increases with exposure to allergens. This "aeroallergen" theory, however, has not been examined in other countries and should be regarded only as an alternative hypothesis.

Identifying Life-Threatening Features

The clinicians who analyzed the 1960s epidemic were impressed by features different from those that impressed the epidemiologists. Rebuck and Read concluded, for example, that misassessment on clinical grounds, failure to use tests of the severity of the disease and undertreatment rather than overtreatment contributed to the increase in asthma deaths.[8] They noted that the first report of any substantial number of blood gas measurements in people with asthma did not appear until 1967, nearly at the end of the epidemic, so they thought it would be valuable to describe the clinical features of patients with severe life-threatening asthma. They reasoned that death occurs from suffocation and therefore focused their efforts on combining assessments of the degree of airflow limitation (the "load"), of arterial oxygen and carbon dioxide tensions (the "outcome") and of the physical cost of the work of breathing. In brief, they considered the clinical features of severe asthma as consequences of airway narrowing, and they identified alveolar hypoventilation, pulmonary hypertension and right heart strain, pulsus paradoxus and hypoxemia as hallmarks of life-threatening asthma.

Many of these hallmarks were present in the patient under discussion. Her pulsus paradoxus was 30 mm of mercury, for example. In Rebuck and Read's study, no patient with pulsus paradoxus greater than 20 mm of mercury had an FEV_1 greater than 40% of their best FEV_1; for most, the FEV_1 was less than 20% of their best (Figure 1). The P_{CO_2} of the patient presented herein was 43 mm of mercury on admission and rose to 60 mm of mercury over the next few hours. In Rebuck and Read's study, the P_{CO_2} was generally in the mid-30s in patients with mild asthma. It was "normal" (40 to 44 mm of mercury) in patients with severe airflow obstruction. Asthma is associated with an increase in the drive to breathing, as if the central thermostat for carbon dioxide has been reset to a lower value. Retention of carbon dioxide is found only in patients whose FEV_1 is severely reduced, usually to well under a liter. A P_{CO_2} of 40 mm of mercury or above on admission is thus a warning sign that the work of breathing is too great for the increased drive to breathing to be met by an increase in alveolar ventilation.

The other clinical features of patients with life-threatening asthma that Rebuck and Read described included exhaustion, any disturbance in consciousness, an FEV_1 of less than 0.5 liter, a forced vital capacity of less than 1 liter and pneumomediastinum or pneumothorax on the chest radiograph. At-

tempts have been made to reduce all of this information to a single number, the "asthma severity index." Fischl's group developed a scoring system in which they assigned one point for each of the following features: a pulse rate of greater than 120 per minute, a respiratory rate of greater than 30, a pulsus paradoxus of greater than 18 mm of mercury, a peak flow of less than 120 liters a minute, dyspnea, accessory muscle use and wheezing.[9] Of 205 conscious patients, the mean score was 5.1 in those requiring admission. Of those who were treated in the emergency department but who returned subsequently because they were unable to carry on at home, the mean score was 4.9. For those who were treated in the emergency department and successfully discharged home, the mean score was 1.6. Thus it appears that a score of greater than 4 on presentation indicates a high risk of relapse even after an apparently successful initial treatment. Subsequent investigators have not confirmed the highly accurate predictive value claimed for the score in Fischl's study, however, perhaps because Fischl's study failed to include the response to initial therapy among the criteria describing whether a patient would need admission.[10] It is nevertheless true that the clinical features of asthma's severity should be systematically noted in patients with acute bronchospasm and should be used in making decisions about the need for admission to hospital.

The publication of criteria for recognizing severe asthma does not mean that they will be used, as Cochrane and Clark showed in their survey of 19 deaths from asthma in London hospitals in 1971.[11] Review of the admitting notes on these patients showed that no physiologic assessment had been done in 15 and peak flow or FEV_1 had been measured in only 4. Blood gas values had been determined in only four patients, and in no case was the fraction of inspiratory oxygen noted. In one patient a Pco_2 of 55 mm of mercury had been recorded but no follow-up blood gas measurements were done. Chest radiographs had been taken in 13 patients; the respiratory rate had been recorded in 7. Only one patient was admitted to an intensive care unit. Steroids had been given to 8 of the patients, but sedatives to 15. In keeping with this sad record of misassessment and inattention, 13 of the deaths occurred between midnight and 8 AM, when nursing and physician surveillance is least intense. Cochrane and Clark's study had the disadvantage of not being prospective and controlled, but its implications seem clear enough. Patients with severe asthma need to be identified early, followed closely and treated effectively. We seem to have taken these warnings to heart, and death from asthma is becoming increasingly rare in patients admitted to hospital. Our pride in this fact needs to be tempered, however, because deaths from asthma appear to be on the rise.

New Zealand Experience

Attention to a possible new epidemic of asthma was first called in New Zealand (Figure 2).[12] It is not really correct to call the increase in deaths a new epidemic, as the death rate in New Zealand never returned to base-line levels at the end of the mid-1960s, but it did take off steeply in 1977. Careful examination of the deaths ascribed to asthma show that this increase cannot be attributed to misdiagnosis or misclassification, suggesting that asthma is more prevalent, more severe or more often fatal.

The New Zealand experience prompted renewed study of asthma deaths in the United Kingdom and in the US. In the decade from 1974 to 1984 in the United Kingdom, the death rate from asthma among patients 5 to 34 years old increased by 4.7% per year.[13] The number of patient visits for asthma increased over the same period by 4% per year, and the number of admissions to hospital for asthma increased by 10%. Drug-induced arrhythmias seemed unlikely as a cause of this increase in death rate, because the number of patients dying within an hour of the onset of symptoms has remained constant at between 20% and 30% over the period of observation. Figures from our National Center for Health Statistics show a similar trend,[14] although they are a little hard to analyze because of the 1979 change in the international classification of disease. With this change, patients who died with asthmatic bronchitis are recorded as having died of asthma, rather than of bronchitis, but this should account for a 35% increase in asthma deaths only between 1978 and 1979. It would not account for the continued increase thereafter, and recent data suggest that the trend continues. In 1978 there were 1,800 deaths from asthma, in 1979 there were 2,600, in 1982 there were 3,100 and in 1984 there were 3,600. The greatest absolute increase has been in the elderly, but the

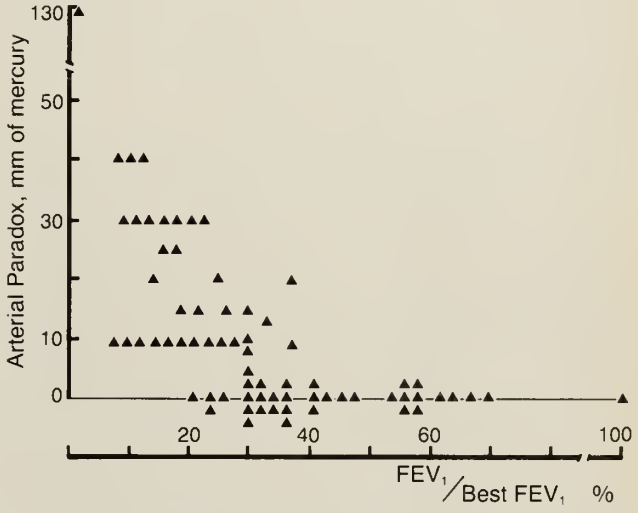

Figure 1.—The degree of arterial paradox is plotted against the forced expiratory volume at 1 second (FEV_1) at presentation, the latter expressed as a percentage of the best FEV_1 ever recorded in each patient (from Rebuck and Read[8]).

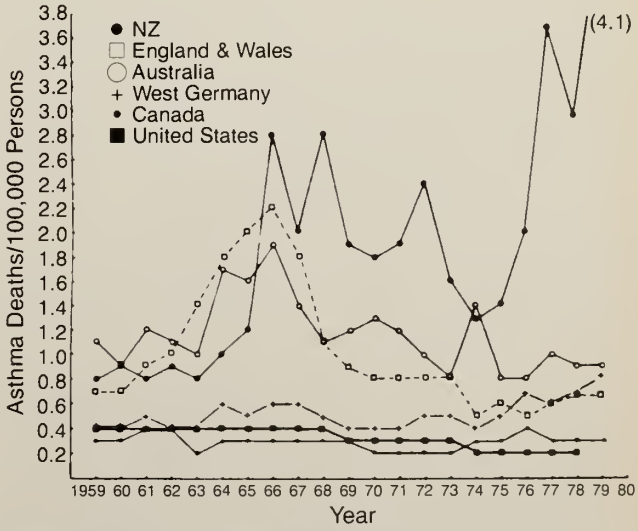

Figure 2.—The graph shows asthma mortality in 5- to 34-year-old persons in six countries during 1959-1979 (from Jackson et al[12]).

greatest proportionate increase has been in children from 10 to 14 years old. This increase in mortality may be linked to an increase in asthma's prevalence. The national hospital discharge survey showed 127,000 hospital admissions for asthma in 1965 and 289,000 in 1983.[13]

In summary, the US data for asthma show that prevalence, the number of hospital admissions and of deaths from asthma have all increased. International data support the idea that the increase in asthma mortality is linked to an increase in prevalence, for the relationship between asthma mortality and prevalence is similar in all of the surveyed nations except Sweden, which did not accept the 1979 change in disease classification (Figure 3).[15]

This is discouraging news, for we think we have effective, safe treatment for asthma, and it is certainly being sold. Figures show great increases in the sales of aerosolized corticosteroids, aerosolized bronchodilators and theophylline between 1975 and 1981.[16] Despite the sales, these drugs do not seem to be as effective as does the therapy for other diseases. In the developed world, striking decreases have occurred between 1951 and 1980 in the death rates from tuberculosis, cervical cancer, rheumatic heart disease, hypertension, stroke, appendicitis and cholecystitis.[17] Over the same period, the death rate from asthma has increased.

Risk Factors for Asthma Deaths

The new epidemic of death in New Zealand prompted much of the same speculation as did the epidemic of the 1960s in Great Britain. Some of the speculation was xenophobic. A few letters to the *The Lancet* suggested that the death rate in New Zealand was due to the adoption of American habits of treatment with theophylline and β-adrenergic aerosols, although the US death rate is substantially lower than that in commonwealth countries. A careful review of 271 deaths from asthma in New Zealand in people younger than 70 suggests another explanation.[18] This retrospective review of those who died suggests that most had features suggesting poor use of care, severe disease or both. For example, the increase in asthma mortality was greatest among those 15 to 24 years old, an age when humans seem least willing to accept the recommendations of established authorities. Race was clearly a risk factor. For the Maori, the native people of New Zealand, the death rate was five times that for whites of European descent, and for Pacific Islanders asthma mortality was three times that for whites. This influence of race on asthma mortality does not appear to be wholly a function of access to or use of care. Race also seems to be a risk factor for developing asthma. Among Pacific Islanders, asthma is three times more common in those living in New Zealand than it is among those who remain on the home islands. Asthma became much more common in New Guinea as it adopted a Western European life-style. The reasons for this are unknown, but it is curious that the increase in mortality should have been noted in New Zealand, a country that is hardly thought of as a polluted, overly industrialized nation.

The study of asthma deaths also showed that the patients who died were more likely to have failed to consult a physician. In all, 103 were judged as having had inadequate maintenance care and 104 to have delayed seeking care. Other features suggested they had severe disease. Many had had previous life-threatening attacks, and many had been intubated for previous attacks. Most had had one or more hospital admissions or emergency department visits within the preceding year, and many used three or more classes of drugs, such as a theophylline, a corticosteroid and an inhaled adrenergic agent.

The same points are made but more poignantly by a retrospective review of a year's asthmatic deaths in New Zealand children between 2 and 14 years of age.[19] There were 16 deaths, and all died outside of hospital. On reviewing the records, 11 of the deaths were judged to have been potentially preventable. Again, the features were inadequate maintenance therapy, underassessment of severity leading to a failure to call for help and, when a call was made, inadequate response of medical services. In the four children in whom failure of assessment of severity seemed important, two had parents who seemed to believe that one should overcome asthmatic attacks by strength of will, and one had a parent who was fatalistic. A prospective study of patients discharged from the National Jewish Hospital (Denver) has confirmed the implications of these findings.[20] Among the patients discharged after admission for asthma, deaths were more common in those classified as having severe disease and disturbances in psychosocial function. Alcoholism and problems with authority were more common in the families of those who died after discharge. The New Zealand survey also showed that inadequate response of medical services was often important. Four children died after being advised by physicians who neither examined them nor suggested that they be seen in an emergency department. One child died after contacting a receptionist who did not want to disturb the physician on call. The children were also considered to have had severe disease. Six were rated as having severe asthma and eight as having moderately severe asthma, but only three had been treated with corticosteroids. Ten had had two or more emergency department visits, and eight had been admitted to hospital within the preceding year. Eight died after a gradual increase in symptoms over a week or longer, but half died with symptoms that lasted for less than six hours. Only two had used bronchodilators excessively, but postmortem examination suggested that they died of asphyxia rather than arrhythmia. Both had severe obstruction and mucus plugging their airways.

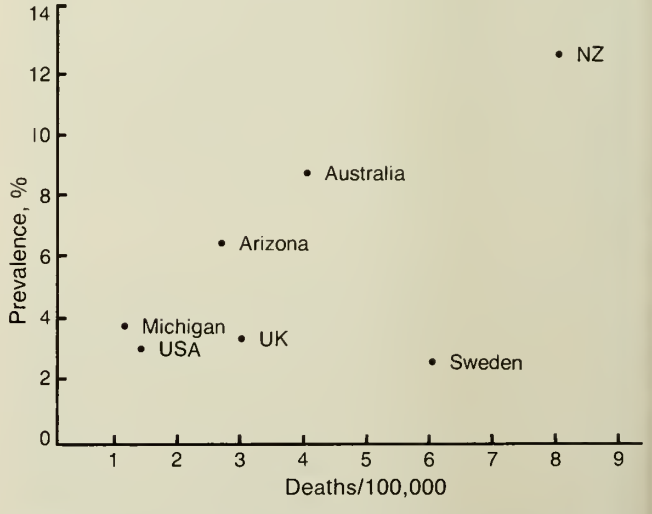

Figure 3.—The graph shows deaths from asthma per 100,000 population in all age groups in 1980 in relation to the prevalence of asthma in New Zealand (NZ), Australia, United Kingdom (UK), Sweden, USA and in Arizona and Michigan (the World Health Organization figures) (from Woolcock[15]).

Educating Patients About Their Asthma

The lessons of the New Zealand experience and of many similar studies in Britain and in the United States are obvious. Patients with asthma requiring hospital admission, intubation and mechanical ventilation, or more than two emergency department visits in a year, need to be taught about their disease and about medication use. Specific instructions should be given about when to seek further care. My practice is to advise patients to treat themselves with a rapidly tapering course of prednisone when their symptoms are uncontrolled and to notify me that they have done so. It is important for patients to be able to call somebody who knows them when they are disturbed about a change in their symptoms and their lack of response to bronchodilator therapy. Formal programs in self-management have been shown to be effective in reducing hospital admissions and emergency department visits for asthma. Examples are asthma camps, the American Thoracic Society's Superstuff Program for children with asthma and formal programs of instruction for adults with the disease.

Educational programs on recognizing symptoms of severe attacks and on the importance of seeking medical attention might prevent many of the deaths from asthma, but we would still be left with those who die abruptly—the 20% to 30% who die within three hours of the onset of their symptoms. That it might be possible to identify these patients was suggested by the study of Hetzel and co-workers of sudden deaths from asthma in hospital,[21] and by Bateman and Clarke's study of deaths in patients followed in a high-risk asthma clinic.[22] Hetzel and associates analyzed 1,169 consecutive patients admitted to hospital for asthma; 458 were recognized as having severe disease and were referred to an intensive care unit. Only one of these patients had a ventilatory arrest, and he was successfully resuscitated. Nine ventilatory arrests occurred among the 711 patients referred to the general medical ward. This does not appear to have been due to a failure to appreciate that they had severe disease by the usual criteria. None had tachycardia on arrival, only one had pulsus paradoxus of greater than 20 mm of mercury and only four had a peak flow of less than 100 liters per minute. What they did have was a greater than 50% diurnal variation in their peak flow. Typically, the troughs in peak flow occurred in the early morning hours, the "morning dipper" pattern. This variability in peak flow disappeared when steroid therapy was increased. In retrospect, it seems possible that the importance of lability in peak flow measurements may not have been noted in the United States because of our greater use of corticosteroids. Of the patients who suffered a respiratory arrest in Hetzel and colleagues' study, only three had been treated with more than 10 mg of prednisone per day. In our hospital, and probably in the United States in general, this would be considered a low dose for patients requiring hospital admission for asthma.

Bateman and Clarke made a similar observation in the patients they followed in a "high-risk" asthma clinic. These were patients who had been identified as being at risk, educated about their disease and encouraged to call if they felt ill. They were even allowed to admit themselves directly to the hospital. Despite all these measures, two patients died. Both were young women who refused steroid therapy for fear of its cosmetic effects and who had highly variable values for peak flow. Another group at risk has been found in a follow-up study of patients who had required admission to hospital, intubation and mechanical ventilation for asthma.[23] One group in whom death occurred after discharge had highly variable values for FEV_1 when they came to the clinic; another group had progressive deterioration in the FEV_1 values from week to week. The notable lability in airflow of the first group was probably a reflection of airway hyperreactivity. Woolcock in Australia analyzed bronchial reactivity in five survivors of nearly fatal asthmatic attacks requiring intubation and mechanical ventilation.[15] All had severe airway hyperreactivity. Over the next two years two of these five died despite intensive antiasthmatic therapy.

There are several practical lessons to be drawn from these studies. One is that we should recognize that the patients at risk include not only those who have required many admissions for asthma, have been discharged within the previous two months, who require three classes of therapy, but also those who have progressive deterioration or striking lability in their pulmonary function test values. Once patients have been identified as being at risk, they must be educated. We might start simply by advising that the risk exists, that there is a risk of dying of asthma. Patients should understand the purpose of different medications and the correct ways of using them. A crisis plan should be developed, emphasizing the availability of emergency department or office treatment. For patients who seem unable to estimate the severity of their airflow obstruction, the portable peak flow meter is particularly useful. Such patients can be taught that peak flows of less than 150 liters per minute indicate severe airflow obstruction and that flows of less than 100 liters per minute indicate an urgent need for treatment.

As to treatment, the recent studies of asthmatic deaths do not implicate aerosolized bronchodilators as a cause of death. These agents are effective and safe, and they should be used as first-line therapy for mild asthma and as a central part of therapy for severe asthma. In a way, their very effectiveness may present a risk, for some patients may find them so effective for most attacks that they delay seeking further attention for the more severe attacks that are less responsive to β-adrenergic treatment. Corticosteroids, particularly inhaled corticosteroids, should be used more commonly in patients at risk. Inhaled corticosteroids improve the symptomatic severity of asthma and reduce bronchial reactivity.[24–26] The doses recommended in the United States are below those that cause systemic side effects or adrenal suppression, and larger doses may be more effective. It also appears that the regular use of inhaled cromolyn for 6 to 18 months will reduce bronchial hyperreactivity. We thus have the means to do something fundamental to the extreme sensitivity of the asthmatic airway that appears to be related to the risk of severe or fatal attacks.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *You commented that you thought that many of the patients dying of asthma in the London hospital study had been treated with insufficient doses of prednisone. What doses do you recommend?*

DR BOUSHEY: Corticosteroids have been used in treating asthma since 1952, but prospective double-blind studies showing their efficacy for status asthmaticus have only recently been published.[27–29] Greater improvement in the corticosteroid-treated groups was not seen for eight hours, so it is not surprising that the patient presented today deteriorated despite treatment over the first few hours of hospital stay. One study showed dose-dependency for methylprednisolone's ef-

fect,[28] and on that basis I recommend 2 mg per kg of body weight be given intravenously every six hours until clinical improvement occurs.

PHYSICIAN IN THE AUDIENCE: *How do corticosteroids act?*

DR BOUSHEY: We don't really know, but corticosteroids may act partly by increasing β-adrenergic responsiveness of airway smooth muscle, perhaps by reversing down-regulation of β-receptors. We don't quite know what they are doing to leukocytes and eosinophils, but they may reduce the secretion of arachidonic acid metabolites by inhibiting phospholipase A_2. It is certainly clear that the mediators elaborated by inflammatory cells can alter the function of nerves, glands and smooth muscle in the airways.

PHYSICIAN IN THE AUDIENCE: *How does the ability of patients to assess the severity of their airflow obstruction compare with that of their physicians?*

DR BOUSHEY: This question has actually been studied, and the patients win.[30] But neither patients nor physicians do very well. If one is following a patient with asthma, particularly a patient recently discharged from hospital, it is important to quantify airflow obstruction objectively. Spirometry should be used routinely at each visit.

PHYSICIAN IN THE AUDIENCE: *Does excessive use of inhaled β-adrenergic agents lead to resistance to their bronchodilator effects?*

DR BOUSHEY: Yes, it does, but not to a clinically important extent. Long-term treatment with β-adrenergic agents shifts the dose-response curve so that it takes a slightly larger dose to produce maximal bronchodilation, but the doses we use clinically are easily sufficient. Therefore, the slight down-regulation in responsiveness is unimportant for a person who takes two to three puffs from a metered-dose inhaler.

PHYSICIAN IN THE AUDIENCE: *Do you see any role for the prophylactic treatment of an asthmatic person in the first few days of an upper respiratory tract infection?*

DR BOUSHEY: Viral respiratory illnesses increase bronchial reactivity in both healthy people and those with asthma. If amantadine is given early enough, the increase in reactivity associated with influenza infection is prevented, but the drug has to be given virtually at the onset of the illness.[31] This has been done in patients in institutions, but it is hard to do in ordinary practice. My policy is simply to inform my patients of the likelihood that their symptoms may worsen with viral respiratory infection, to advise them to be quick to start treatment with inhaled β-adrenergic agents and to call me if that is insufficient. For well-informed patients with severe disease, I often advise them to initiate short, tapering courses of prednisone on an "as needed" basis, letting me know by telephone when they have done so.

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Epitomes
Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Use of Ipratropium Bromide in Chronic Obstructive Pulmonary Disease

INHALED ANTIMUSCARINIC AGENTS (atropine sulfate, atropine methylnitrate, ipratropium bromide) can partially relieve airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) by reducing vagally mediated bronchomotor tone. Ipratropium bromide (Atrovent) in metered-dose inhaler form has recently been approved by the Food and Drug Administration for use as a bronchodilator in COPD. Bronchodilation following the use of ipratropium occurs within minutes (slower than with adrenergics) and lasts four hours or more (comparable with adrenergics). Maximal bronchodilation is achieved with metered doses of 40 to 80 μg; the recommended therapeutic dose is two actuations (20 μg per actuation) of the metered-dose inhaler. The major therapeutic advantage of ipratropium (a quaternary ammonium derivative) over atropine (a tertiary ammonium compound) is its poor absorption after inhalation, so that few atropinic side effects occur even with large doses. In therapeutic doses, it has no significant effect on mucus production, viscosity or clearance and, unlike β_2-selective agonists, it does not cause tremor.

A recent double-blind multicenter trial of ongoing therapy with metered doses of ipratropium (40 μg) versus metaproterenol sulfate (1,500 μg) four times a day for 90 days in patients with COPD showed a significantly greater magnitude and duration of bronchodilation in the ipratropium-treated group, which was sustained throughout the three months of the study. Side effects from both agents were infrequent, but tachyphylaxis, obvious with the β-agonist, was less evident with ipratropium. These findings, together with similar results from several smaller-scale studies, support consideration of ipratropium as a first-line bronchodilator in the maintenance treatment of COPD.

Although a large dose of either an antimuscarinic or a β-agonist compound administered alone produces maximal bronchodilation in patients with COPD, at least one study has shown additive bronchodilation in these patients when conventional therapeutic doses of ipratropium and a β-agonist were combined. Further studies are required to evaluate the advantages of combining ipratropium with a β-agonist or theophylline (or both) in the long-term management of COPD.

In patients with atopic asthma, unlike in those with COPD, antimuscarinic agents often cause less bronchodilation than do β-agonists; consequently, ipratropium should be considered a second-line bronchodilator in treating allergic asthma.

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The Questionable Value of Routine Admission Urinalyses

TWO RECENT STUDIES questioned the value of the time-honored routine admission urinalysis. Both studies were conducted on internal medicine wards, and both concluded that the impact on patient care of routinely analyzing urine specimens on admission was very small. The findings support the recommendation of the American College of Physicians that no diagnostic tests should be required as routine procedures for patients admitted to hospital.

The major reasons for the test's small impact on patient care are the relatively low diagnostic yield and the even lower likelihood that detected abnormalities represent true disease. By definition, routine admission urinalyses are done for patients without signs or symptoms of urinary tract disorders. Because the prevalence of disease in this group is low, the predictive value of a positive test—the probability that an abnormality represents true disease—also will be low. In addition, many patients admitted to hospital have diseases unrelated to the urinary tract in which transient, self-limited urinary abnormalities are common. Unfortunately, physicians usually cannot tell which findings represent false-posi-

tive results or self-limited abnormalities without additional, otherwise unnecessary, diagnostic testing.

Hundreds of millions of urine specimens are analyzed in the United States each year, costing consumers billions of dollars. It appears that doing these tests based on clinical findings and not simply on hospital admission could decrease medical care costs with little adverse effect on patient care.

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Diagnosing Pulmonary Embolism

THE ORIGINAL UROKINASE STUDY showed that the clinical diagnosis of pulmonary embolism was not specific enough to justify the risks of anticoagulant therapy: only 162 of 906 patients suspected of having pulmonary embolism had it confirmed angiographically. Subsequently, with quantum improvements in the technology of the perfusion lung scan and the development of a clinically useful ventilation scan, there was widespread use of the combined ventilation-perfusion lung scan for clinical decision making. Unfortunately, no prospective, randomized clinical trial had ever been done to validate the concepts of matched and mismatched scan patterns. This overreliance on the ventilation-perfusion lung scan was the subject in 1977 of a controversial editorial in the *Annals of Internal Medicine*. Much of the literature that appeared after the editorial continued to report results on series flawed by selection bias and other problems. Only one large prospective series studying the sensitivity and specificity of lung scan patterns has been reported, and another is in progress. Before commenting any further, I will review some background information on the risks of anticoagulant therapy.

Heparin use is associated with a 5% to 20% rate of hemorrhagic complications and about a 0.5% to 1% fatality rate. Oral anticoagulation with warfarin sodium is associated with complication rates essentially identical to those mentioned for heparin. Because present recommendations are that patients with venous thrombosis, pulmonary embolism or both are treated with both regimens sequentially, the morbidity and mortality are cumulative. In contrast, pulmonary angiography has a 4% major morbidity rate and a 0.25% fatality rate. Also, the careful use of selective, magnified views allows angiography to be used more safely in patients previously thought to be at high risk, and the refinement of nonionic contrast media may further reduce the risk for renal toxicity.

One large prospective study of the relative sensitivity and specificity of various ventilation-perfusion lung scan patterns found that 86% of "high-probability" scans were associated with an abnormal angiogram, whereas 25% to 40% of "low-probability" scans were associated with abnormal angiograms. Perhaps one of the most important results of this study was the finding of such a "high" prevalence of pulmonary embolism in patients with low-probability scans. The study has been criticized for: a possible low case acquisition rate, routinely doing impedance plethysmography of the lower extremities before referring for scanning and angiography, failure to do angiography in all patients who were scanned, using a new, nonstandard ventilation-perfusion scan classification scheme and an overall high prevalence (55%) of venous thromboembolism in all scan categories. Regardless of these criticisms, this is the only modern, prospective comparison of lung scans and angiography available. The Prospective Investigation of Pulmonary Embolism Diagnosis, sponsored by the National Institutes of Health, is not yet completed.

When the uncertainties associated with the various scan patterns are considered and the risks of treatment with anticoagulant drugs are compared with those of angiography, many physicians believe there is a compelling argument to expand the indications for angiography. Based on available information, clinicians should not rely entirely on the ventilation-perfusion lung scan for decision making in patients felt to have pulmonary embolism, but should strongly consider further diagnostic testing, such as pulmonary angiography or tests to document deep vein thrombosis, as the treatment is essentially the same. Obviously, no single set of recommendations can possibly address the myriad permutations of patient presentations, but the available data indicate that relying on lung scans alone will lead to overtreatment of some patients with false-positive high-probability scans and undertreatment of some with false-negative low-probability scans.

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'Routine' Preoperative Laboratory Testing

PATIENTS ADMITTED TO HOSPITAL for an elective operation commonly undergo a battery of "routine" preoperative laboratory testing. This often includes a complete blood and platelet count, prothrombin time, partial thromboplastin time, electrolytes, blood urea nitrogen, creatinine and glucose levels, urinalysis, chest x-ray film and an electrocardiogram. The goal of such examinations is to detect asymptomatic diseases not apparent on a history and physical examination, which if found and treated appropriately before a surgical procedure would minimize the morbidity and mortality accompanying the operation. Recent studies of such clinical practices have found little scientific support or justification for this goal.

The problem lies in the ability of such tests to detect disease processes in otherwise healthy persons in whom the prevalence of such illnesses is low. Examining just the blood tests that are routinely done (12 in number and assuming "normal" to be the mean value of each test in presumably nondiseased persons plus or minus two standard deviations), in only 54% of all healthy persons screened will all 12 test results be in the "normal" range. Thus, the generation of

many false-positive abnormalities is inherent to the statistical assumptions of normalcy for each test and has no actual clinical benefit. Repeat confirmatory and further diagnostic tests to pursue such abnormal laboratory values also contribute to the costs of such screening. Preoperative laboratory testing has been projected in one study to cost about $4.2 million for each life lost. In an era of increasing cost-containment, such funds could be spent more efficiently to save more lives.

Similarly, the usefulness of more expensive preoperative tests, such as the electrocardiogram and chest x-ray film, to detect asymptomatic illnesses capable of affecting the surgical outcome has proved to be minimal in clinical studies of young, otherwise healthy patients. Unnecessary delays in a surgical procedure and the concomitant patient anxiety for the workup of benign diseases (for example, the asymptomatic granuloma presenting as a lung nodule) also contribute to the inadequacies of these tests. In the elderly in whom the number of diseases and their prevalence increase, chest radiographs and electrocardiograms may be more helpful.

Even when such preoperative laboratory tests are ordered, physicians fail more than half the time to note the abnormalities in the chart and to order follow-up tests.

These studies provide evidence that, in the absence of specific clinical indications, "routine" preoperative laboratory testing can be safely eliminated. Because it has been estimated that 50% of all surgical procedures in this country are done on presumably healthy persons, the potential cost savings would be enormous. It is reassuring to know that the "best test" preoperatively in minimizing surgical morbidity and mortality is still a careful history and physical examination.

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Weight Control in Managing Hypertension

NUMEROUS EPIDEMIOLOGIC STUDIES have shown a relationship between body weight and hypertension; weight gain increases the risk of hypertension developing. The mechanisms responsible for hypertension in obese patients remain obscure. Neither increased plasma volume, cardiac output, salt intake nor altered adrenergic mechanisms are adequate explanations alone. Obesity increases the cardiovascular risk; part of this increased risk can be ascribed to its association with hypertension. An additional risk occurs because of an increased cardiac output. Both hypertension and an increased stroke volume can contribute to the development of left ventricular hypertrophy and left ventricular failure. Weight loss in both moderately obese and morbidly obese persons will result in a significant reduction of blood pressure and the regression of left ventricular mass.

A lowered blood pressure occurs both in patients who have not received medication for hypertension and those who are already receiving medication. There is no linear relationship between weight loss and blood pressure reduction. It has been suggested that there is a "floor" in the blood pressure, so that the blood pressure will not reduce further despite continued weight loss. It is not clear at what level of weight reduction a floor in the blood pressure will be reached, but even a moderate weight reduction of 5 to 7 kg (10 to 15 lb) will produce a significant improvement in blood pressure control. This degree of weight loss will be more easily achieved than will a return to an ideal body weight. As many as 39% of hypertensive patients can remain normotensive for as long as four years without medication if a weight loss of 5 kg or more is coupled with reduced salt and alcohol intake.

The control of obesity is an important variable in managing patients with hypertension. Physicians should attempt to motivate their patients to lose weight if they are obese. If they succeed, better blood pressure control with fewer antihypertensive drugs should be the result.

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Relaxation Therapy for Hypertension

THE WORD "HYPERTENSION" to most patients implies a condition related to increased stress that by some mechanism results in an elevation of the arterial pressure. Although the role of stress as an etiologic factor in the development of hypertension remains a controversial issue, the effective application of relaxation therapy in managing hypertension is becoming clearer. In recent years nondrug therapies have been increasingly advocated in the initial management of mild hypertension, especially when the diastolic blood pressure remains in the range of 90 to 94 mm of mercury. Furthermore, nonpharmacologic approaches are a useful adjunct in treating moderate or severe hypertension and lead to the use of fewer medications in lower doses. Even though the morbid outcomes from untreated hypertension have not been shown to be lowered by the use of nonpharmacologic therapy, these interventions are generally accepted on the basis that they are not associated with significant risks or side effects.

There are more than 60 published studies on the use of transcendental meditation, yoga, several biofeedback techniques and teaching muscular relaxation in the therapy for hypertension. Most studies have shown a small but statistically significant reduction in systolic and diastolic blood pressures in the range of 2 to 10 mm of mercury, but several have shown only transient effects. The lack of carefully controlled studies using random assignment and blinded measurements and the absence of follow-up beyond eight months in most studies raise serious concerns about the effectiveness of these techniques in a clinical setting.

The first long-term follow-up study of relaxation therapy for mild hypertension was recently published in the *British Medical Journal*. In the original study, 204 patients with newly recognized untreated hypertension were randomly assigned to a relaxation program or a control group with fol-

low-up only. The intervention consisted of eight weekly one-hour group biofeedback sessions and prescribed muscular relaxation techniques twice a day at home. Of the 107 persons assigned to the experimental group, 99 accepted the treatment, and at eight months of follow-up they had a mean reduction in blood pressure of 16.2/6.8 mm of mercury compared with 5.0/0.3 mm of mercury for the control subjects. A four-year follow-up of 86 experimental and 75 control subjects found that the effectiveness of relaxation therapy was maintained at a reduced level. The subjects who had been taught relaxation therapy had a mean reduction of 7.2/3.7 mm of mercury compared with a mean increase in the control group of 1.6/4.1 mm of mercury. Although only 14 of the 86 participants practiced relaxation at least weekly, most (63%) practiced it occasionally.

The mechanism by which relaxation therapies lower blood pressure has not been extensively studied, but may be mediated by lowering of the plasma levels of catecholamines, renin and aldosterone. Patients' expectations may also have a significant role in the effect observed with relaxation training, and a subset may exist of hyperresponsive persons who are likely to benefit. In some of the published studies, less than half of the patients were willing to continue relaxation therapy for more than a few months, and thus it is likely that in clinical practice only a minority of patients having hypertension will actually benefit.

The Health and Public Policy Committee of the American College of Physicians recently concluded that biofeedback is a second-line nonpharmacologic therapy for hypertension. Relaxation training is cheaper, easier to implement and has a greater chance for a wider application in clinical practice. Nonphysician health professionals such as nutritionists and psychologists need to be involved in implementing the nonpharmacologic management of hypertension. Teaching relaxation therapy, including the use of commercially available audiotapes, can play an important role in a multicomponent non-drug approach to treating hypertension.

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Postprandial Hypotension

ANGINA PECTORIS AND SYNCOPE occur in some patients after large meals. In one study, a standardized breakfast for patients aged 75 to 98 years produced a mean fall in the systolic blood pressure—taken in the sitting position—of 13 mm of mercury within 35 minutes after ingesting the meal; a group of subjects aged 18 to 37 years had no significant reduction in blood pressure.

We have found that a meal produced a mean reduction in the supine diastolic blood pressure in normal subjects aged 19 to 31, associated with a reflexive increase in the mean heart rate. In patients with hypertension, a meal also reduced the mean supine diastolic blood pressure, associated with an increase in heart rate. Patients with autonomic dysfunction have a much more dramatic change in blood pressure after meals, averaging a decrease of 49 mm of mercury in the supine systolic blood pressure. Decreases as great as 98 mm of mercury have been seen.

The meal size appears to be an important determinant of hemodynamic effects, and meals with a higher protein content may have greater effects. Ingesting food increases the splanchnic blood flow and decreases total peripheral resistance, probably due to a decreased splanchnic resistance.

In many studies, elderly patients have been observed to have a greater hypotensive response to meals. In these studies, however, the blood pressure was higher in the older patients, and the magnitude of the reduction in blood pressure after the meal was also related to the premeal blood pressure.

Ingesting food lowers both systolic and diastolic blood pressures. Elderly patients, patients with hypertension and patients with autonomic insufficiency tend to have the greatest reductions in blood pressure. The hemodynamic effects of meals may contribute to postprandial syncope and to postprandial angina because of a reflex tachycardia and decreased coronary perfusion pressure. More commonly, blood pressure changes of 5 to 20 mm of mercury related to meals may contribute significantly to an apparent blood pressure lability and may seriously impair the interpretation of blood pressure control in patients with hypertension.

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'Unloading' Therapy for Heart Failure

VASODILATOR THERAPY can provide substantial benefits to some patients with congestive heart failure. The rationale is based on the physiologic principles of reducing ventricular afterload and preload (hence the term "unloading" therapy). This results in an increased cardiac output and decreased systemic and pulmonary venous pressures. Symptoms of hypoperfusion and congestion are ameliorated. The peripheral vascular tone (both arterial and venous) is increased in most symptomatic patients with congestive heart failure. An increased systemic vascular resistance and resistance to left ventricular ejection by arterial vasoconstriction reduces the forward stroke volume and cardiac output. Venoconstriction contributes to congestive symptoms by increasing pulmonary and systemic venous pressures; the intracardiac volume is also increased. The vasodilator drugs with predominantly arteriolar effects, such as hydralazine hydrochloride, minoxidil and nifedipine, increase cardiac output. Venodilators, such as nitroglycerin, nitrates and molsidomine, can decrease systemic and pulmonary venous pressures. Vasodilator agents with balanced arteriodilator and venodilator properties—angiotensin-converting enzyme inhibitors and α-adrenergic blocking agents—produce hemodynamic effects similar to those of combinations of arteriodilators and venodilators.

During congestive heart failure, abnormalities of neuroendocrine function contribute to a heightened peripheral vascular tone. Elevating levels of circulatory catecholamines reflect increased sympathetic activity. Plasma renin activity is increased in about two thirds of patients who have chronic

congestive heart failure. This leads to increased production of the vasoconstrictor angiotensin II and increased release of aldosterone and norepinephrine. In some patients, arginine-vasopressin levels are also higher than normal. Vasoconstriction mediated by these neuroendocrine systems are, to some extent, counterbalanced by increased production of vasodilator prostaglandins and the vasodilator, atrial natriuretic peptide. In most symptomatic patients, however, the vasoconstrictor influences predominate, causing a net increase in systemic vascular tone.

Vasodilators have a variety of mechanisms of action. These include the following: antiadrenergic drugs (α-receptor blocking agents, in particular), β_2-receptor agonists, vasopressin antagonists, serotonin antagonists, prostaglandins, calcium entry blocking agents, angiotensin-converting enzyme inhibitors and the direct-acting vasodilators. Hemodynamic studies using these agents usually show initially improved systemic hemodynamics and cardiac performance. Long-term clinical benefit, however, does not occur with all vasodilators. Direct-acting arteriolar vasodilators such as hydralazine or minoxidil, when used alone, do not improve the exercise capacity or clinical state significantly in patients with chronic congestive heart failure. α-Receptor blocking agents such as prazosin hydrochloride are also ineffective in most patients. In contrast, isosorbide dinitrate and the angiotensin-converting enzyme inhibitors, captopril or enalapril maleate, improve the clinical state and exercise tolerance in most patients. Recently a Veterans Administration cooperative trial has reported that a combination of hydralazine, 300 mg a day, and isosorbide dinitrate, 160 mg a day, can improve survival of patients with mild to moderately severe chronic congestive heart failure.

Based on these reports, either a combination of hydralazine with nitrates or angiotensin-converting enzyme inhibitors should be considered in the "unloading" therapy for chronic heart failure. A lack of comparative studies prevents making a clear choice between these approaches, although correcting neuroendocrine abnormalities more effectively by using angiotensin-converting enzyme inhibitors may favor the latter.

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Treatment of Gram-Negative Bacterial Meningitis

THE THIRD-GENERATION cephalosporin antibiotics have greatly improved the prognosis for adult patients with gram-negative bacillary meningitis. Before 1980, when aminoglycoside antibiotics and chloramphenicol were used extensively, case-fatality rates ranged from 40% to 90%. Since the third-generation cephalosporins were introduced, case-fatality rates have fallen dramatically; in fact, cure rates of 75% to 90% have become the rule. Of these agents, cefotaxime sodium and moxalactam disodium have received the most usage for this indication. Available data suggest that ceftriaxone sodium, ceftazidime and ceftizoxime sodium offer comparable efficacy. These antibiotics show potent bactericidal activity against not only *Escherichia coli* and *Klebsiella pneumoniae*, the leading pathogens, but also against many other Enterobacteriaceae. Minimum inhibitory concentrations range from 0.01 to 1.0 μg per ml for most genera of this family except *Enterobacter*. In patients with meningitis, drug concentrations in cerebrospinal fluid (CSF) greatly exceed these minimum inhibitory concentrations: peak concentrations generally range from 10 to 40 μg per ml. Thus, unlike aminoglycoside antibiotics or chloramphenicol, third-generation cephalosporins produce CSF antibiotic concentrations that are 20 to 100 times the minimum inhibitory concentration of the infecting bacterium, and they rapidly sterilize the CSF.

Despite the successes of third-generation cephalosporins, meningitis caused by certain species of gram-negative bacilli remains a difficult and somewhat controversial therapeutic problem. The most troublesome organisms include the more resistant Enterobacteriaceae, such as *Enterobacter cloacae*, as well as certain non-Enterobacteriaceae, notably *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus*. Therapy for infections caused by these organisms is optimally based on the results of quantitative susceptibility tests. As a general rule, when minimum inhibitory concentrations of the third-generation cephalosporins for the pathogen are greater than 1.0 μg per ml, patients require the most active third-generation cephalosporin or extended-spectrum penicillin plus the most active aminoglycoside antibiotic. Trimethoprim-sulfamethoxazole may be useful against some organisms, such as *A calcoaceticus*. Aminoglycoside antibiotic administration by both intravenous and intralumbar routes is recommended. Intraventricular administration through a reservoir should be considered for patients who have relapsed or responded poorly to other regimens.

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Home Intravenous Antibiotic Therapy

HOME INTRAVENOUS (IV) ANTIBIOTIC THERAPY presents an opportunity to provide hospital level therapy at a substantially lower cost while enabling patients to resume a near-normal life-style.

Proper patient selection is the cornerstone of successful home therapy. Patients appropriate for home treatment have no indications for hospital care other than the need to receive antibiotics intravenously. Common infections treated are osteomyelitis, septic arthritis, diabetic foot infections, endocarditis (after inpatient observation) or any other conditions wherein patients are medically stable except for an infection requiring IV administration of antibiotics.

Efficacy is the primary consideration for antibiotic selection in any treatment setting, but one must additionally adjust dosing times to accommodate patients' sleep patterns and use

regimens that minimize infusion frequency. Cefazolin, cefonicid sodium, cefoperazone sodium and ceftriaxone sodium are used extensively because their infrequent dosing requirements, safety and spectrum match many conditions amenable to home therapy.

A competent, effective IV therapy team is another critical component of this technique. IV therapists need to have both expert nursing skills and knowledge regarding potential toxicity. They must remain readily available to patients on a 24-hour basis and possess strong teaching skills so that patients develop confidence and judgment.

Issues still to be standardized are the optimal organization of home care agencies, patient and diagnosis qualification criteria, standards of care for physicians and agencies, reimbursement and liability exposure.

In the final analysis, home IV therapy makes sense in today's thrust toward providing as much care as is safe and feasible outside hospital. It synergizes with the public impulse to accept more responsibility for personal fitness and health. To invoke this new modality, physicians need only blend their current expertise and sound medical judgment with the special considerations for home therapy summarized above. When home IV antibiotic therapy is done well, everyone benefits.

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Vaccination for Hepatitis B

TWO SAFE VACCINES containing purified hepatitis B surface antigen (HBsAg) are now available for preventing hepatitis B infection. The first vaccine is derived from the plasma of screened, healthy HBsAg carriers. Even though extensive tests show that all known viruses are inactivated by the vaccine preparation process, many patients and health care providers have been reluctant to use this plasma-derived vaccine because of concerns about the acquired immunodeficiency syndrome. The second vaccine, released in early 1987, is prepared from recombinant DNA propagated in yeast. The recombinant vaccine, because it is not plasma derived, has had greater acceptance but has no other advantages and has a similar level of safety and cost. Concerns about long-term efficacy of the yeast-recombinant vaccine have been raised because of reduced antigenicity when compared with plasma-derived HBsAg.

Protective levels of antibody to HBsAg develop in about 85% to 95% of vaccinated healthy adults, who receive three doses of vaccine intramuscularly in the deltoid. Antibody levels tend to be lower if the injections are given in the buttock or to patients who are immunologically compromised. For those who have the usual anti-HBsAg response, protection approaches 100%. The duration of protective antibody levels is not yet known and booster doses may be required at some future time.

There are no known adverse or beneficial effects to vaccinating previously infected persons. Thus, the decision to screen potential vaccinees (using either hepatitis B core antigen or anti-HBsAg) is an economic one, based on the cost of screening tests and vaccination versus the likelihood that a patient has previously had hepatitis B.

Hepatitis B vaccine is recommended for persons at increased risk of hepatitis B developing. Potential vaccinees include homosexually active men, users of illicit injectable drugs, hemodialysis patients, selected immigrants, prisoners, institutionalized retarded persons, recipients of factor VIII or IX concentrates, long-term transfusion recipients, household and sexual contacts of hepatitis B carriers and health care workers with frequent exposure to blood or blood products.

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Intraperitoneal Chemotherapy for Ovarian Cancer

OVARIAN CANCER is the most common fatal gynecologic malignant disorder in the United States and the fourth leading cause of cancer death in women, with 18,000 new cases and 11,000 deaths per year. About 80% of patients with ovarian cancer have advanced disease (stage III or IV) at diagnosis. With the introduction of cisplatin-based combination chemotherapy administered systemically, surgically documented complete response rates of 20% to 30% can now be achieved. Few of these responses, however, result in long-term relapse-free survival (seven-year survival rate less than 15%).

Ovarian cancer is a disease that tends to remain confined to the peritoneal cavity even in its most advanced stages. This makes it particularly amenable to regional methods of drug delivery. A recently developed technique for treating advanced ovarian cancer has been the direct intraperitoneal administration of chemotherapeutic agents. One of the major principles of intraperitoneal chemotherapy is to administer the anticancer agent in a large fluid volume of a normal saline solution (two liters) to ensure adequate drug distribution throughout the peritoneal cavity. Another is to administer agents known to be active against ovarian cancer when administered systemically. With intraperitoneal administration, high drug concentrations can be achieved in the area of the tumor while corresponding systemic levels are much less, resulting in less drug exposure to normal tissues. This results in an enhancement of the drug's therapeutic index. We have used a totally implantable drug delivery system for intraperitoneal drug administration in our studies. It consists of a Tenckhoff catheter attached to a Port-a-Cath portal (Pharmacia Nu Tech).

The most active single agent for the treatment of ovarian cancer is cisplatin. We have conducted a series of intraperitoneal cisplatin-based chemotherapy trials over the past several years. Agents that we have used in combination with cisplatin have included cytarabine and, most recently, etoposide. These studies have been done in patients with persistent disease following administration of at least six cycles of intravenous cisplatin-based chemotherapy. Two important conclusions have emerged from these studies. First, the intra-

peritoneal administration of chemotherapy does not appear to be superior to administering it intravenously in patients with bulky intraperitoneal disease. In patients with small-volume disease (tumor nodules less than 2 cm in diameter), however, the results have been excellent, with 70% of patients alive, with a median follow-up of 29 months and with an apparent plateau on the survival curve. These results are superior to any other published data in patients with refractory ovarian cancer.

These encouraging results need to be confirmed in prospective, randomized clinical trials involving a much larger number of patients. The Southwest Oncology Group is currently conducting a prospective clinical trial in which patients with previously untreated stage III ovarian cancer (disease confined to the peritoneal cavity; tumor nodules less than 2 cm in diameter) are being randomly assigned to intraperitoneal cisplatin-containing chemotherapy or intravenous cisplatin-containing chemotherapy. Many single-arm clinical trials of intraperitoneal chemotherapy have been initiated over the past two years at a number of university medical centers. In addition, based on the above encouraging results, intraperitoneal administration of cisplatin is being more widely used in community practice for ovarian cancer patients with refractory, small-volume disease confined to the peritoneal cavity.

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Bone Marrow Transplantation as Primary Treatment of Leukemia

CONSIDERABLE PROGRESS HAS BEEN MADE during the past ten years in the treatment of acute and chronic myelogenous and acute lymphoblastic leukemia using bone marrow transplantation.

In the initial trial of *allogeneic* bone marrow transplantation in patients with relapsed acute myelogenous leukemia by the Seattle transplant team, a long-term relapse-free survival of 13% was achieved in patients for whom all prior therapies had failed. When patients, however, were transplanted earlier in the course of their disease—in first remission—relapse rates dropped to 15% to 20% and overall survival is now 40% to 50%. Because chemotherapy for acute myelogenous leukemia has been improving and the complications of bone marrow transplantation have remained significant, the role and timing of allogeneic transplantation have been questioned.

The success of allogeneic bone marrow transplantation in the treatment of acute myelogenous leukemia was recently confirmed by three randomized studies of transplantation versus chemotherapy. These studies all show a greatly decreased risk of relapse but considerable mortality due to graft-versus-host disease and concurrent infections following bone marrow transplantation in comparison with consolidation chemotherapy. As a result, overall survival is better following bone marrow transplantation, but the complication rate remains high. Further success will depend on the improved abrogation of graft-versus-host disease and fewer infectious complications. Attempts to decrease graft-versus-host disease by T-cell depletion of the donor marrow have been successful in abrogating the reaction but have unfortunately been complicated by higher rates of fungal infection, a greater risk of graft rejection and a higher risk of leukemic relapse.

Autologous transplantation for patients with acute myelogenous leukemia in both first and second (or third) remission avoids the risk of graft-versus-host disease but has a potentially higher relapse rate than allogeneic bone marrow transplantation. Preliminary results indicate that 25% to 40% of patients in first remission may achieve at least one year of disease-free survival following ablative chemotherapy and reinfusion of marrow harvested and frozen while in remission. Autologous transplantation of marrow purged of residual leukemic cells with 4-hydroperoxycyclophosphamide has resulted in a two-year disease-free survival of 40% for patients with acute myelogenous leukemia in second or third remission.

For patients with chronic myelogenous leukemia there had been no hope for cure and no improvement in survival with any form of standard therapy since George Richards Minot introduced splenic irradiation in the 1920s. Now data clearly show that allogeneic bone marrow transplantation will provide a 50% to 60% relapse-free survival in patients with chronic myelogenous leukemia in chronic phase. Results are better the earlier the transplant is done after diagnosis and when patients are younger than age 30. Especially encouraging is the absence of Philadelphia chromosome-positive cells as long as five years after transplantation. When patients reach the accelerated phase of chronic myelogenous leukemia or an overt blast crisis develops, disease-free survival drops to 15%. Results of autologous transplants for chronic myelogenous leukemia have been uniformly poor thus far. Using partially matched siblings with T-cell depletion of the donor marrow or matched unrelated donors has had limited success, but complications such as increased rates of graft rejection and relapse have limited this to an experimental approach at present.

Allogeneic transplantation for acute lymphoblastic leukemia has not been as successful, primarily because of a high posttransplant relapse rate (60%). Changes in the conditioning chemotherapy regimen may improve the outcome. A relapse-free survival rate of 30% in children in second remission and without human leukocyte antigen-matched donors has been achieved by using monoclonal antibodies to common acute lymphocytic leukemia antigen to deplete autologous marrow of leukemic cells.

The use of improved conditioning regimens to decrease the possibility of relapse, new ways of treating the marrow to purge it of T cells or leukemic cells and enhanced prevention of posttransplant infections will enable more patients with leukemia to be treated successfully. In time, partially matched and unrelated transplants will also become practical. Ultimately, it should become possible to culture pure marrow stem cells, avoiding graft-versus-host disease entirely.

Current recommendations would include allogeneic bone

marrow transplantation in first remission for patients younger than 40 years who have acute myelogenous leukemia, autologous bone marrow transplantation for patients between the ages of 40 and 55 with acute myelogenous leukemia or for those younger than age 40 without a matched donor, allogeneic marrow transplantation for patients younger than 50 years with chronic myelogenous leukemia in the chronic phase and allogeneic transplantation for patients younger than 40 years with relapsed acute lymphoblastic leukemia.

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Physician-Patient Communication

RECENT SOCIAL SCIENTIFIC RESEARCH has clarified certain social structural barriers to physician-patient communication. Practicing internists spend little time giving information to their patients (about 1.3 minutes on the average in encounters lasting about 20 minutes), overestimate the time they spend giving information (by a factor of about nine) and underestimate their patients' desire for information. College-educated patients and those with upper- or upper-middle-class occupations generally receive more information than do patients who have not gone to college or who hold working-class occupations. There is no difference between poorly educated, lower-class patients and better educated, upper-class patients in their desire for information. Physicians, however, misperceive this desire much more commonly for poorly educated or lower-class patients. Busier internists who see more than 20 patients per day spend much less time giving information and also give a smaller number of explanations. Because adequate communication takes time, this finding has implications about the number of patients whom physicians should reasonably see per day in clinical practice.

Another fruitful direction of research has focused on nonverbal communication and the sociolinguistic structure of physician-patient encounters. When physicians are skillful at decoding body movement and postural cues to emotion (as measured by tests of nonverbal communication ability), their patients show higher levels of satisfaction and compliance. Interestingly, physicians' expression of nonverbal tension in encounters is positively associated with patients' satisfaction and compliance, probably because it conveys a strong task orientation to which patients respond favorably. Physicians frequently interrupt patients during encounters; usually these interruptions involve physician-initiated questions. Such a "high-control style" may have counterproductive effects in history taking, especially when it leads physicians to overlook nontechnical concerns that patients feel are important in their everyday lives. Interrupting behavior also may reflect sexual differences in language use, because female physicians tend to interrupt their patients much less frequently than do male physicians.

Training programs should emphasize the potentialities for improving physician-patient communication. In particular, physicians should know that patients frequently want more information than practitioners realize and that sociolinguistic differences in language use can impede effective communication. Nonverbal communication skills and the highly structured, interrogative mode of the medical history also deserve reconsideration in medical education.

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On Reducing Health Care Costs

Two "Epitomes" (our title for the section on "Important Advances in Clinical Medicine") appearing in this issue question the value and the costs of routine urinalysis on admission to hospital and routine laboratory testing before an operation in hospital. Both these kinds of tests have been almost standard procedure for many years, and indeed looked upon almost as a standard of care, as well as a dependable source of revenue for laboratories and for hospitals. But, as the authors point out, there is little evidence that these more or less hallowed customs are of any benefit to patients. In fact, quite the opposite, these tests when done routinely, may call attention to borderline or nonexistent abnormalities which, if not ignored by the clinician physician, may lead to further tests, usually unnecessary, with attendant risk, discomfort and cost to a patient, the cost most often being borne by the third party who pays for the care.

These findings are important both in terms of costs and what is really good patient care, or quality care, to use what is becoming a well-worn phrase. Quality care is generally thought of as costing more, and no doubt it generally does. But it is more than likely that there are many situations where quality care may actually cost less. Certainly routine tests that have been shown likely to create more problems than they solve or prevent are examples of this. The real "bottom line" of patient care is quality care at the lowest cost, and when this conflicts with the "bottom line" of anyone's fiscal balance sheet, the professional duty should be obvious enough. The bottom line of quality care should prevail over the bottom line of costs. But it is equally obvious that quality care that really costs less merits more study, attention and action on the part of members of our profession, working as closely as possible together with all others who may be concerned. Serious attention to this could help to reduce the overall costs of health care.

MSMW

Duodenal Ulcer Disease—Lessons From History

Among physicians old enough to remember, duodenal ulcer disease is not what it used to be. Younger physicians, unfortunately, are not apt to recognize any difference. For both, the thoughtful and incisive review of Mulholland and Debas elsewhere in this issue provides a valuable perspective on the lessons learned from the study of this disease. Since the lessons of history are neither easily learned nor readily appreciated, however, I have focused on three lessons that illustrate the challenge of dealing with duodenal ulcer disease or with other maladies with similar vagaries. These lessons show us what can be learned by studying epidemiology, drug therapy and the problems of surgical treatment.

First let us consider epidemiology. There is a convenient dichotomy in clinical thinking that goes like this: Infectious diseases are, by their nature, quick to appear and to spread. Our expectation is that suitable environmental and immunization programs will be developed to either control the disease or make it go away. The acquired immunodeficiency syndrome is a case in point. From modest beginnings in the jungles of Central Africa, it has grown to occupy the national consciousness, and the predictions of its continued growth are dire. We wait in anxious anticipation for an immunization program to save us. The epidemiology of the disease is lost on no one.

On the other hand, diseases such as inflammatory bowel disease, prostate cancer, osteoporosis and appendicitis are considered immutable for all intents and purposes. Yes, there may be different incidences of these diseases at different places, and even small changes over time in a given location, but, for the individual practitioner, such changes appear to be so small as to be imperceptible or, if recognized, inconsequential.

The first lesson to be learned from duodenal ulcer disease is that our latter perception may be wrong. Diseases which we have previously considered to be unchanging are, in fact, evolving. As noted by the authors, the first indication of a decrease in the incidence of peptic ulcer disease was noted in the late 1960s and early 1970s. In retrospect, the incidence had been in decline for about a decade at that point. Widespread appreciation of the change, however, did not come about for another decade. In the interim, hospitals and physicians had experienced great changes in their activities. There were fewer hospital admissions for duodenal ulcer disease and fewer and fewer operations done. A major clinical disease was disappearing and the impact on physicians and hospitals was profound. The change was totally unexpected and appreciated only in retrospect.

But why unexpected? Duodenal ulcer disease had not *always* been a major clinical problem. Its rapidly increasing incidence had been noted in the 1920s, and by the 1940s predictions were being made that it would affect nearly 10% of the American male population. Thus, the expectation was for a continued increase in the incidence of the disease—not a decrease. We have believed that this category of disease does not change. But ulcer disease has shown us that change can and does occur and that the effects are pronounced.

One wonders, then, why we do not track diseases more carefully. Professional societies given to one discipline or another regularly discuss investigations on all aspects of a given disease without noting if the incidence of the disease is, in fact, increasing or decreasing. Our ability to gather and collate relevant information has greatly improved in the recent past, and more timely and more widespread information on the epidemiology of disease may be in order.

The second potential lesson is something more, for the development of the histamine H_2-receptor antagonist is one of the more fascinating stories in clinical medicine. A direct attempt was made to develop a drug that would specifically block histamine's action on the parietal cell. We started with histamine itself and, after a decade of effort, remarkable success was achieved with the introduction of cimetidine. As the authors indicate, it has revolutionized the treatment of duodenal ulcer disease. Perhaps more importantly, however, these drugs have also contributed to our understanding of the complex physiology of the parietal cell. While the interaction and interdependence of secretagogues on the parietal cell have been known, the advent of powerful blocking agents began when it was shown that action on one of the receptor sites blocked actions on other sites, providing a tool to investigate the relative potencies of these agents. The success in blocking

the parietal cell receptor to histamine suggests that selective blocking of the receptor to gastrin, another important secretagogue site, may be possible. Efforts in that direction have already been made.

Unfortunately, the histamine-receptor antagonists have proved to be misleading in at least two ways. First, convenience and efficacy have fostered a feeling of invincibility. The drug always seemed to work. Only slowly has it become evident that failures with histamine-receptor antagonists are both possible and more frequent than had been appreciated. Second, the drugs are remarkably (and disarmingly) effective in relieving symptoms. The prompt relief of ulcer symptoms in 48 to 96 hours after beginning therapy is the rule rather than the exception. Prospective endoscopic examinations of duodenal ulcers show that healing of an ulcer requires at least a week of treatment and that only slightly more than half are healed at the end of two weeks. Small wonder, then, that the drugs are considered uniformly effective in curing ulcers. Yet, as Mulholland and Debas have clearly stated, there remains an important clinical need to gauge when treatment with a histamine H_2-receptor antagonist has failed.

The epitome in specific blockage of acid secretion has been achieved with the development of the substituted benzimidazole class of drugs, exemplified by omeprazole. Omeprazole shuts down the production of hydrogen ions by the parietal cell. It does so by adhering strongly and solely to the proton pump, the producer of the ions. The drug can render patients achlorhydric for considerable periods of time. But do we really need or want to do that? It is not clear what effect such powerful agents will have on the integrity of the gastric mucosa over time. Too much of a good thing may not be too good at all.

Lastly, the perspective supplied by the authors on the surgical treatment of duodenal ulcer disease provides an important lesson on the difficulties of altering clinical practice. The attributes which lead to the wide adoption of one operative procedure but not another are not understood. In the 1970s, when parietal cell vagotomy was both widely studied and used in England and Europe, it was virtually ignored in the United States. Even now, only a few surgeons are knowledgeable and competent in this operation. Yet, in that same time-frame, jejunoileal bypass for obesity was widely practiced in the United States without benefit of much study, while being completely rejected abroad. One wonders at the discrepancy. Surgical practice much like therapy with H_2 blockers is not entirely directed by relevant information.

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Bacterial Meningitis in the 1980s, or One Drug or Many?

IN THE FIRST HALF of the 1980s, we witnessed the introduction and proof of efficacy of the new group of antimicrobial agents in the treatment of the various forms of bacterial meningitis. The extensive bibliography in the article by Drs Ampel and Labadie elsewhere in this issue will inform readers of how great the activity was in this area. Such a time of change in antibiotic introduction and usage is always a confusing one. For example, moxalactam has come and gone in clinical practice without a formal obituary notice in the literature.

At this juncture several changes have clearly occurred. Chloramphenicol has been dethroned by general acclamation as an overall first- or second-line therapeutic choice for the wide range of meningeal pathogens. This drug is no longer considered appropriate for treating enteric gram-negative bacillary meningitis or for *Listeria*, and its killing kinetics for pneumococci have long been uncertain. Finally, skepticism has replaced optimism about chloramphenicol's penetration into the cerebrospinal fluid (CSF). The only uncontested area where its use still holds is in the treatment of *Hemophilus influenzae* meningitis. Meanwhile, the lightly regarded cephalosporins, whose molecules were not believed to reach the CSF, were found to reach it through inflamed meninges even more effectively than do the penicillins.[1] At this point the newer cephalosporins are considered the major agents for the treatment of bacterial meningitis.

It was not always so. Ten years ago they were considered inactive and inappropriate, which indeed they were.[2] It was not so much a question of their poor penetration into the CSF but of their lack of activity against *H influenzae*[3] and against *Neisseria* and some of the other major meningeal pathogens. This, however, was true only of that group of early cephalosporin molecules, which are now curiously termed "first-generation cephalosporins."

Cefuroxime was the first agent in this group of β-lactams to attract attention and extensive use in Europe in the treatment of meningitis,[4,5] largely on account of its strikingly enhanced activity, as compared to the older agents, against *H influenzae* and *Neisseria*. It was used both as therapy for enteric gram-negative pathogens and as empiric initial therapy in pediatric meningitis. Nevertheless, some caution was voiced in the beginning about its therapeutic margin of safety for the common meningeal pathogens. This translates into how many multiples of the minimal inhibitory concentration or, better yet, the minimal bactericidal concentration of the potential pathogens are possibly attainable in the CSF. Because miscalculated, late or missed doses are always possible, and indeed even likely, prudence can be important in designing antibiotic therapy. Indeed, several poor responses to cefuroxime therapy have been recently reported.[6] The introduction and widespread clinical use of cefotaxime and subsequently of ceftriaxone, whose enhanced activity provides a far higher therapeutic margin, have rendered further debate irrelevant. Enteric gram-negative meningitis ranks a poor fourth, in comparison to *Streptococcus pneumoniae, H influenzae*, and *Neisseria meningitidis*, as a meningeal pathogen in this country. Nevertheless, it was in this area of usage that cefotaxime and moxalactam showed their usefulness, probably as a consequence of the newly demonstrated lack of effectiveness of chloramphenicol.[7] Today cefotaxime and, by extension, ceftriaxone are considered the agents of choice for the group of pathogens comprising *Escherichia coli, Klebsiella, Salmonella* and the proteus group.[8] For *Enterobacter*, the results are less good; at least half of the cases fail to respond.[8] It is here that trimethoprim-sulfamethoxazole or gentamicin given intrathecally (or both therapies) can be extremely useful. *Pseudomonas* meningitis, usually a sequela of prolonged neurosurgical procedures, can often be successfully treated with ceftazidime, prudently supplemented by gentamicin parenterally or, better, intrathecally, since relapses have occurred with the use of ceftazidime as monother-

apy.[9] Further, ceftazidime monotherapy for infections of other body sites has led to the emergence of strains of *Pseudomonas* resistant to this drug.[10]

The present state of things has been ably summarized in Table 1 of the article by Ampel and Labadie. Other considerations pertain in Europe, where the primary therapeutic approach is often that of using cefotaxime as initial empiric therapy for all cases of meningitis before isolation and sensitivity testing of the organism.[11,12] A similar pattern of use was previously noted for cefuroxime in the same area. There is a problem in this form of therapy. None of the available cephalosporins are adequately active against *Listeria monocytogenes*, an infrequent meningeal pathogen in this country (although several recent dairy outbreaks may eventually challenge this generalization). In the dairy farm areas along Europe's northeastern coast, *L monocytogenes* is an important pathogen in neonates, pregnant women and immunosuppressed patients. We have asked several colleagues from that area what they do in this circumstance. Apparently for such high-risk groups, they just add amoxicillin to the cefotaxime regimen.

How can one explain this radical difference in patterns of antibiotic use? Our European colleagues make the following points: First, the limitations of the newer cephalosporins—that is, lack of effectiveness against *Listeria* and enterococci—are minor compared with the limitations of ampicillin (amoxicillin) or chloramphenicol. Second, the age-related separation of pathogens is hardly absolute. Adults can have *Salmonella* or *H influenzae*,[13] just as children can have pneumococcal meningitis.[12,14] Last, the ordinary diagnostic measures that we recommend in cases of meningitis are subject to error. A far higher percentage of cases than we would like to admit has negative Gram's stains or fails to produce positive cultures. Immunologic methods are most useful for *H influenzae* meningitis, but of little help for other forms of meningitis. Even when smears are positive, the correct diagnosis may not be made. Another reason for this difference in practice may lie in the nature of the clinical practice of pediatrics or infectious disease in large parts of Western Europe as compared with the United States. The separation of the hospital from office practice has progressed much further in Europe than it has in the United States. The hospital staff is full time, the hospitals are quite large and the infectious disease and pediatric specialists often have primary responsibility for 50 to 100 beds in the larger centers. In short, after the nth case of meningitis, what does one want with a complicated therapeutic schema? In this country few infectious disease specialists or pediatricians have primary clinical care responsibility for more than a few such cases each year. Hence, complicated schemas are possible. If my observations are correct, we should detect a future tendency toward a unitary initial therapy in the larger clinical centers in this country. Perhaps in a few years' time, Ampel and Labadie will again have to revise their therapy table, signifying an even greater change in antibiotic usage.

In summary, the past five to ten years have been a period of considerable change in our patterns of use of antibiotics for meningitis. Cephalosporins achieve significant antibiotic concentrations in the CSF of patients with meningitis, and several have sufficient activity to be of broad use in treating the four most common meningeal pathogens: pneumococci, *H influenzae*, meningococci and the enteric gram-negative rods. Chloramphenicol is now viewed as having a limited role and that only in treating bacteria for which it is bactericidal. Indeed, it is now conceded that to successfully treat meningitis (as to treat endocarditis) one must choose a bactericidal drug. Well, almost always! Those *Listeria* again! Neither ampicillin nor penicillin is reliably bactericidal for *L monocytogenes*, at least in the concentrations achievable in the CSF.[15,16] An aminoglycoside needs to be added to achieve that in the test tube. Yet, ampicillin and penicillin work even as monotherapy, and it is hard to show that adding an aminoglycoside clinically changes the response rate.[7]

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The Chief Complaint

IN PATIENT CARE the "chief complaint" gives the first indication of why a patient may be seeking a physician's help. Sometimes the chief complaint relates to the obvious. "I cut my finger." "I am allergic to cats but I love my cat." But sometimes the relationship between the chief complaint and what is really wrong may not be so direct or obvious. "I have a pain in my belly." "I have headaches all the time." "I have pains around my heart." And if one is privileged to take care of a physician or a nurse, the chief complaint and the description of symptoms (1) may be a model of professional accu-

racy, (2) may be a textbook description of something they believe they have but do not or (3) may have nothing to do with the real problem, all the pertinent information having been suppressed for one reason or another. In short, the chief complaint may be direct and to the point; it may be an important guidepost, opening the way to a correct diagnosis and treatment, or it may be a smokescreen hiding the real trouble and sometimes, though rarely, it may be actually misleading.

There appears to be a perception in today's society that there is something wrong with the medical profession. Somehow the profession is not what it used to be. We hear the complaints. "Health care costs too much." This comes mostly from those who have to pay the bills. In the same vein, the chief complaint of the public against the medical profession may well be that "doctors make too much money." Is this last complaint direct and to the point? After all, the average income of physicians in this nation is said to be in the neighborhood of $100,000 a year. Or might it be a point of departure that could open the way for a dialogue leading to a more complete diagnosis of the real concern? Or could it be a smokescreen hiding an unspoken but deeper dissatisfaction? One wonders whether it might not be all of the above.

But is the perception that physicians make too much money really all there is to the problem? One senses that it is not. Some physicians make a lot more and some make a lot less. And given the amount of training involved and the amount of responsibility entailed, annual earnings of $100,000 may not be all that far out of line. After all, this is about what commercial airline pilots are said to make. Perhaps it would be worthwhile to attempt to open a dialogue to try to reach a diagnosis—that is, to try to find more accurately what it is the public perceives to be wrong with the medical profession. After all, this is what physicians do in professional practice when they begin to evaluate someone's chief complaint in their offices.

The profession has substantial skills when it comes to discovering what it is that underlies a patient's chief complaint. These skills involve listening to what a patient has to say, taking a careful history, doing a careful hands-on examination, and actually measuring whatever can be measured that might help with the diagnosis or treatment. But it is noteworthy that all this occurs within the well-known framework of a doctor-patient relationship. The patient has a problem and the physician tries to find the cause and then attempts to do something about it. But there has to be a professional interaction between physician and patient—that is, the physician must be in the role of physician to the patient or the process will not occur and the cause of the chief complaint will not be found.

To return to the societal complaint that "doctors make too much money," one may ask where is the doctor-patient relationship between the medical profession and the society it serves? Where is the process for dialogue to try to discover the real reason for the complaint? It does not seem to exist. To enlarge upon this, could it be that society as a whole somehow senses that it has lost its physician and that this is really what is wrong, and therefore a fundamental cause of disaffection with the medical profession? Even if this is the case for society as a whole, it is worth noting that this may not be so true in smaller communities, where local physicians not only take care of patients in a very personal way but in the aggregate they actually serve as "physician" to the community by participating in community affairs, studying local health problems and giving needed and respected consultation and guidance to the community.

One can only wonder if a truly professional examination of the "chief complaint" we have selected—that is, "Doctors make too much money" or any other such complaint for that matter—might be used as a point of departure for some sort of a professional diagnostic process, adapting traditional diagnostic skills in such fashion so as to begin to understand what really underlies some of these societal complaints. The medical profession has the training to find a way to do this. It would only be necessary to develop a diagnostic approach that would in some way parallel what physicians do when they examine a patient's complaint in their everyday practice. If this were done successfully, the profession would have developed a new approach to better address some of the problems of health care in today's society. Organized medicine could then begin to play the role of physician to society, even while investigating complaints that might lead to the very realization that the profession should indeed play this role. It seems reasonable to believe that, just as in some smaller communities, the role of physician to society by organized medicine, on a local, state or national scale, could be powerfully effective, and in both the profession's and the public's interest.

MSMW

Catheter-Related Thrombophlebitis of the Superior Vena Cava Caused by *Candida glabrata*

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ALTHOUGH FUNGEMIA occurs frequently in patients with central venous catheters, fungal thrombophlebitis of the superior vena cava and other great veins appears to be a rare complication. Only a few cases are reported in the medical literature, virtually all caused by *Candida*.[1-3] In this report we describe a case of catheter-associated fungal thrombophlebitis of the great central veins caused by *Candida glabrata* (formerly, *Torulopsis glabrata*). It emphasizes the role of computed tomography in diagnosis and, in this case, the success of medical therapy alone in its management.

Report of a Case

The patient, a 59-year-old man with steroid-dependent chronic obstructive pulmonary disease, entered the hospital because for three weeks he had had lower abdominal pain and symptoms of hyperglycemia. Although he had no history of diabetes mellitus, his blood glucose level at that time was 575 mg per dl. Following several diagnostic studies, the patient was taken to surgery where a large abscess adjacent to a perforated colonic diverticulum was found. He underwent drainage of the abscess, segmental colectomy and creation of an end-colostomy with a mucous fistula. Culture of specimens from the abscess yielded only *Escherichia coli*. The patient's management also included 11 days of subclavian vein catheterization for intravenous hyperalimentation, an intravenous insulin drip for several days and broad-spectrum antimicrobial therapy for 10 days. Before entering the hospital the patient had been taking 5 mg of prednisone twice a day. During this hospital stay he received 300 mg of hydrocortisone per day intravenously in the perioperative periods with rapid tapers back to maintenance levels (25 mg hydrocortisone per day or 5 mg prednisone per day) thereafter.

Following his first operation the patient progressed satisfactorily until the 24th hospital day, when abdominal pain recurred and an enterocutaneous fistula was detected. A subclavian vein catheter was placed for a second time and intravenous hyperalimentation was resumed. Computed tomography of the abdomen after the patient had several episodes of fever showed a left lower quadrant fluid collection. Broad-spectrum antimicrobial therapy was restarted and the patient had surgical drainage of a large pelvic abscess and repair of three associated perforations of the small bowel. Culture of specimens of the abscess yielded only *Klebsiella oxytoca*.

From the time of the second operation on hospital day 42 until day 59, the patient's course was characterized by daily spiking fevers and accompanying systemic toxicity. Culture of a specimen of blood that had been drawn on the 39th hospital day was reported positive for *Candida glabrata* in the immediate postoperative period. Fungemia persisted—cultures of 24 blood specimens drawn on 15 different days between hospital days 39 and 59 were positive for this organism. Four of these blood cultures were also positive for coagulase-negative staphylococci.

Management of the bloodstream infection consisted of administering antimicrobial agents, changing central venous catheters and repeatedly searching for other foci of infection; none were ever identified. *C glabrata* was cultured in a specimen of drainage from the abdominal wound or associated

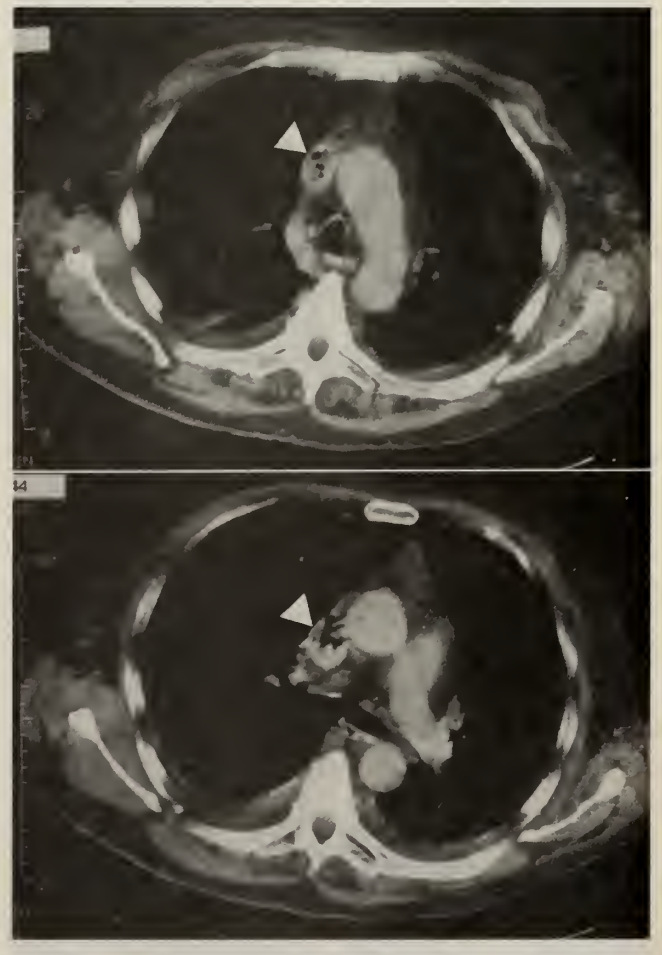

Figure 1.—Computed tomography done on the 59th hospital day, 50 seconds after contrast injection, shows, **top**, a low-density thrombus containing multiple gas bubbles in the superior vena cava **(arrow)** at the level of the aortic arch and, **bottom**, thrombus and extensive gas bubbles filling the lumen of the superior vena cava **(arrow)** at the level of the left pulmonary artery. (Other cuts revealed thrombus extending into the right atrium and subclavian veins.)

(Paige C, Pinson CW, Antonovic R, et al: Catheter-related thrombophlebitis of the superior vena cava caused by *Candida glabrata*. West J Med 1987 Sep; 147:333-335)

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drain sites on hospital days 24, 42, 48 and 58; these wounds were not infected at the time. The organism was not recovered from urine, sputum or abscess fluid. Amphotericin B therapy was begun on the 44th hospital day. The patient's systemic toxicity diminished somewhat, but fungemia persisted for another 15 days. Vancomycin therapy was initiated on the 49th hospital day and blood cultures rapidly became negative for staphylococci. Central lines, considered essential for hyperalimentation, were maintained in the left and right jugular veins throughout this period, though they were changed frequently and rotated from side to side in response to the continuing report of additional positive blood cultures. About half of the line changes were done over guide wires. Tips from the removed catheters were cultured three times during this period—on the 45th, 50th and 56th hospital days. The first culture was sterile, the second yielded more than 100 colonies of *C glabrata* alone and the third yielded more than 100 colonies of both *C glabrata* and coagulase-negative staphylococci.

On the 59th hospital day computed tomography of the thoracoabdominal region was carried out with contrast enhancement. This examination showed extensive thrombosis and associated gas formation extending from the entrance of the right atrium through the superior vena cava to both subclavian veins (Figure 1). Physical examination failed to disclose any signs of superior vena cava obstruction, but the radiologic findings, together with persistent fungemia, were interpreted as diagnostic for fungal thrombophlebitis of the great veins. Hyperalimentation was discontinued and all central venous catheters were removed permanently. Amphotericin B therapy, 50 mg every other day (about 0.3 mg per kg per day), was continued and heparin therapy was started. Echocardiography at this time did not show any vegetations on the patient's cardiac valves.

Figure 2.—Computed tomography with contrast enhancement done before discharge shows residual thrombus in the midportion of the superior vena cava **(arrow).** (The crescent-shaped low-density structure adjacent to the anterior wall of the ascending aorta is the superior pericardial recess.)

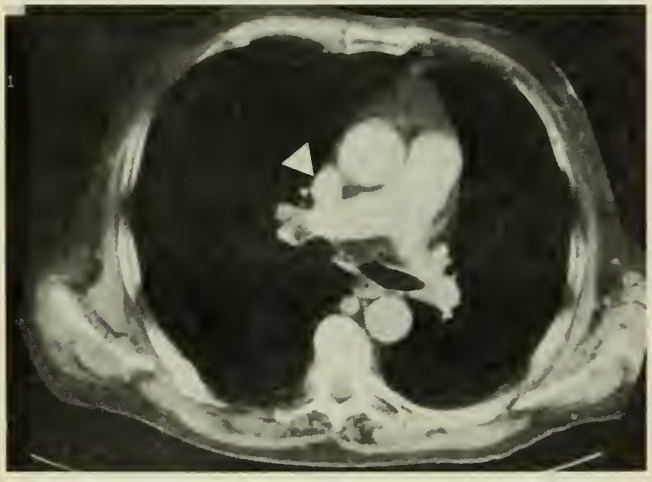

Figure 3.—Computed tomography with contrast enhancement done three months after discharge shows normal superior vena cava **(arrow)** at the level of the right pulmonary artery.

Following the changes made on the 59th hospital day, the patient's condition began to improve. His fever remitted, systemic toxicity resolved, blood cultures became negative and convalescence proceeded without complication. Amphotericin B therapy was continued until the 105th hospital day, for a total course of 1,675 mg (19.4 mg per kg). Anticoagulation was maintained with a regimen of warfarin sodium, which was ultimately administered for about six months. Computed tomography done before the patient's discharge on the 106th hospital day showed considerable improvement in the superior vena cava, though some clot remained (Figure 2).

The patient continued to do well after discharge and, in what is now six months of outpatient follow-up, he has shown no evidence of lingering or metastatic infection. Repeated examinations have failed to disclose any signs of endophthalmitis. A computed tomographic examination of his chest done about five months after the original one showed complete resolution of disease in the superior vena cava and other great veins (Figure 3).

Discussion

Serious nosocomial infections caused by *Candida glabrata* have occurred with increasing frequency in recent years. This yeast, which is smaller than other species of *Candida* and lacks mycelial forms,[4-6] inhabits a variety of environmental niches in addition to the stool, skin, oral cavity and vagina of healthy persons.[7] Although once considered relatively avirulent, during the past 15 years *C glabrata* has been recognized as an opportunistic pathogen in immunocompromised and debilitated patients. Our patient showed several risk factors associated with *C glabrata* infections: diabetes mellitus, corticosteroid therapy, a major operation, broad-spectrum antibiotic therapy, hyperalimentation and central venous catheterization. Other recognized risk factors include malignancy, transplantations, profound neutropenia, alcoholism and immunosuppressive or antineoplastic chemotherapy.[4,8] *C glabrata* may have entered the bloodstream of our patient through the bowel, by absorption or by traumatic injury related to a surgical procedure and perforations or through the skin at the site of one or more intravenous lines. These portals of entry and the urinary tract have received most attention in reported cases of fungemia.[9] Our patient had no evidence of urinary tract involvement, transient or otherwise.

Diagnosing fungal septic thrombosis is difficult, especially in the absence of endophthalmitis or localized edema indicating venous obstruction. Serologic tests, indium-labeled leukocyte scans and even blood or urine cultures are not reliable indicators of infected clot.[1] The presence of the previously mentioned risk factors, a persistent low-grade fever despite removal of intravenous lines and a deteriorating clin-

ical state are associated with serious *C glabrata* infections in contrast to transient catheter-related fungemia.[8]

In the absence of biopsy specimens from the superior vena cava or other involved veins, a diagnosis of fungal thrombophlebitis in our patient remains somewhat conjectural. From a clinical standpoint, however, the evidence for this diagnosis is compelling. First, our patient had persistently positive blood cultures for *C glabrata* over a period of 20 days despite more than two weeks of intravenous antifungal therapy and numerous replacements of his central venous catheters. These data strongly suggest the presence of a fixed intravascular focus of infection. No extravascular focus or evidence of endocarditis was ever detected. Second, the appearance of the superior vena cava and other great veins on computed tomography attested not only to the presence of extensive thrombosis but also to the likelihood of infection within the clot itself—microbial growth in the clot matrix is the most likely explanation for the observed gas bubbles. *C glabrata* metabolizes glucose to produce gas, and gas was observed throughout the entire length of clot. Schmitz and co-workers have reported a case of septic thrombophlebitis of the inferior vena cava due to toothpick perforation, with gas bubbles in the thrombotic material.[2] Finally, our patient's course paralleled that of other reported cases in which the evidence for fungal thrombophlebitis of the great veins was more direct.[1]

In reported cases the diagnosis of thrombophlebitis involving the superior vena cava and other great veins has usually been established by contrast venography.[1,10] Computed tomography with contrast can also be used to establish this diagnosis. This technique has been used to diagnose venous diseases in other vascular beds: inferior vena cava,[2] portal venous system[11] and jugular venous system.[12] Characteristic findings of thrombotic disease include enlargement of the vessel lumen, the demonstration of collateral vessels, enhancement of the vessel wall and the presence of a nonenhancing filling defect within the vessel lumen.[11,12] Ring enhancement, which is sometimes observed, is due to dilation of the vasa vasorum. Our patient's initial scan showed many of these findings plus gas bubbles in the clot, a finding probably due to microbial metabolism. Because computed tomography is much less invasive than venography, it may prove to be more useful for the initial evaluation of patients with possible thrombophlebitis of their great central veins. As our experience indicates, computed tomography can also be used to follow the course of the disease and the response to therapy even in the absence of clinical manifestations of venous obstruction.

The therapy for thrombophlebitis involving the great veins differs radically from that for thrombophlebitis of peripheral veins—surgical excision of the affected vein is considered mandatory in the latter condition,[13] especially when fungi are involved.[14] As our case shows, however, medical therapy alone may suffice for patients with infection of the great central veins,[10] even when fungal disease is present.[1] Prolonged courses of antimicrobial agents with or without concurrent anticoagulation therapy have been used successfully in most reported cases regardless of the cause. Removal of the venous catheter has also figured prominently in management.

Our patient's case resembles those of the eight patients with *Candida* thrombophlebitis of the great central veins associated with central catheters reported by Strinden and colleagues.[1] Our patient's risk factors and disease manifestations were similar, and, like six of their eight patients, he was cured with intensive medical therapy alone. This case report brings a unique species of *Candida* into the spectrum of causes of thrombophlebitis of the great central veins. Most important, it shows the value of computed tomography in diagnosis. This case also suggests that permanent catheter removal and anticoagulant therapy are needed in addition to antifungal therapy to cure this type of infection.

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Wound Botulism

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WOUND BOTULISM is a rare disease. During the past 11 years (1976 through 1986), 19 cases have been reported to the Centers for Disease Control (CDC) through their botulism surveillance program and requests for botulism antitoxin. These 19 cases of wound botulism occurred in 9 states: 8 in California, 3 in Washington, 2 in Texas and 1 each in Maryland, Pennsylvania, New York, Tennessee, Arizona and Wyoming (MacDonald and co-workers[1] and an oral communication January 16, 1987, with Andrew T. Pavia MD, CDC, Atlanta). Before 1976 (1943 to 1945), 15 cases of wound botulism had been reported, all associated with traumatic extremity injuries.[2] We report a case of wound botulism (Wyoming, 1986) that occurred in a young man after he sustained a puncture wound to his foot associated with a retained foreign body (wood splinter).

Report of a Case

The patient, a 21-year-old man with alcoholism and a history of intravenous (IV) abuse of cocaine, was brought to

(Swedberg J, Wendel TH, Deiss F: Wound botulism. West J Med 1987 Sep; 147:335-338)

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
IV = intravenous
P_{CO_2} = partial pressure of carbon dioxide

the emergency department because of sore throat, dysphagia (unable to swallow liquids), progressive weakness and diplopia. Twelve days before admission, he had been given dicloxacillin sodium and a tetanus booster by a community physician for the treatment of cellulitis of his right ankle and lower leg. The cellulitis occurred four days after the patient sustained a puncture wound to his right heel while at a local lake. About nine days before admission he noted blurred vision, and three days later he had the onset of diplopia, sore throat, mild dysphagia and malaise. Three days before admission, he had increasing soreness and dryness of his throat, associated with increasing dysphagia and dysarthria and progressive weakness (upper extremities greater than lower extremities). He said he did not have nausea, vomiting or diarrhea. He had not eaten home-canned foods, and all foods that he had consumed in the past week had been shared with others who remained in good health. The patient admitted to drinking six cans of beer per day and to using cocaine (intravenous administration) four to five times during the past year. He reported that his most recent use of cocaine was at least a month earlier. Tetanus immunization was recorded as complete.

On examination on admission he appeared disheveled, dehydrated and somnolent, but was easily aroused and oriented. His voice was of low amplitude with dysarthric speech. He was afebrile (temperature 36.4°C [97.5°F]) and had mild hypertension (blood pressure 128/104 mm of mercury). His pupils were dilated 5 to 6 mm but equal and reactive to light. There was some weakness of the extraocular muscles—predominantly the lateral rectus muscles—on both sides and the patient complained of diplopia. His lips were dry and crusted, and he was unable to protrude his tongue past his teeth or to open his mouth more than 1 to 2 cm. The posterior pharynx was dry and red but without exudates. His neck was supple and nontender but he had pronounced weakness of neck flexors (unable to raise his head from the bed). His right ankle had a slightly indurated and mildly tender darkened area just inferior to the lateral malleolus, but no cellulitis or lymphadenopathy was evident. The patient's skin was carefully examined, especially at sites of previous IV drug administration. No other significant skin lesions or evidence of infection was found. His neurologic examination was most remarkable for weakness—diminished lateral eye movement, bilateral palatal weakness, inability to protrude tongue past teeth and neck flexure weakness. He also had weakness of his arms, most notable proximally, making it an effort to raise his elbows from the bed. He said he did not have paresthesias, and on examination his sensory system was completely intact. Deep tendon reflexes were preserved, with normal reflexes in the upper extremities and brisk knee jerks—slightly greater on the right than the left—associated with four beats of clonus on the right.

After the patient's admission, his weakness was observed to progress with the development of prominent ptosis of both eyes and a symmetric descending paralysis involving the respiratory musculature and the lower extremities. On the second hospital day, his condition—hypoventilation with a partial pressure of carbon dioxide (P_{CO_2}) rising to 85 mm of mercury—required ventilatory support; an endotracheal tube was introduced and he was put on a respirator.

At the time of admission, hydration given intravenously was started, and the intravenous administration of penicillin, 1 million units every four hours, was begun. Initial laboratory studies showed a normal leukocyte count of 5,700 per μl, a hematocrit of 53.7% and a hemoglobin of 18.1 grams per dl; he had a sedimentation rate of 6 mm per hour. A urine toxicology screen was negative. Arterial blood gas determinations indicated a pH of 7.44, partial pressure of oxygen 61 mm of mercury and P_{CO_2} 40 mm of mercury. Computed tomography of the head was within normal limits. A cerebrospinal fluid specimen obtained by lumbar puncture was normal except for a slightly increased protein level of 50 mg per dl (normal 25 to 50). A repeat lumbar puncture on the fourth hospital day provided similar values—protein of 43 and glucose of 78 mg per dl, and 10 cells (2 leukocytes and 8 erythrocytes) and no organisms were seen. An edrophonium chloride test was done on the second and again on the fourth day after admission without abatement of the patient's weakness. In addition, a serum specimen evaluated for acetylcholine receptor binding and blocking antibodies was normal. Electrophysiologic studies done on the 2nd hospital day and repeated on the 22nd hospital day showed a decreased amplitude of the evoked muscle action potential after a single supramaximal nerve stimulus and a definite incremental response after repetitive stimuli.

A specimen of the patient's serum was sent to the CDC for mouse toxin neutralization testing (Enteric Bacteriology Section, Division of Bacterial Diseases, Center for Infectious Diseases, CDC, Atlanta, GA 30333; telephone [404] 329-3867). When the mice were given 0.8 ml (double dose) of the patient's serum, there were signs of botulism and then death in the mice that had not been pretreated with trivalent antitoxin. There was insufficient serum left to type the botulism toxin. An additional specimen of the patient's serum was requested and obtained several days later but did not contain detectable botulism toxin. Specimens of the patient's stool did not have botulism toxin present and *Clostridium botulinum* was not identified on culture. On the third hospital day, trivalent (types A, B and E) botulism antitoxin was given to the patient. The puncture wound in the right lateral heel was surgically explored with the patient under general anesthesia. A small sinus tract with necrotic tissue was noted, but no pus was evident. *Pseudomonas* and a *Candida* species were identified on cultures of specimens of the wound site.

On the 11th hospital day a tracheostomy was done and the patient remained on a respirator until the 34th hospital day, when he was successfully weaned from the ventilator. His respiratory status continued to improve and he was discharged on the 37th hospital day.

Three months after his initial admission, the patient presented with increasing tenderness over the previous puncture site. The site was again explored surgically (right lateral heel and ankle) and a 1-cm wood splinter was removed from an area just proximal to the peroneal brevis insertion and running along the peroneal tendon. *Pseudomonas* was identified on aerobic cultures. No growth occurred on anaerobic cultures, but these specimens were noted by laboratory personnel to have been improperly handled. No Gram's stain was done. The wood splinter in formalin, however, was later sent to the botulism laboratory at the CDC. A small amount of sediment was recovered by centrifugation and examined microscopi-

cally using fluorescent antibodies to type A and type B *C botulinum*. No fluorescent staining material was found.*

Discussion

Of the 19 cases of wound botulism reported in the United States from 1976 through 1986, 15 (79%) occurred in the western United States, 14 (74%) patients were male and the mean age was 24 years (range 7 to 65 years). The diagnosis was made postmortem in one of the reported cases, but in the remaining 18 cases, 13 (72%) required ventilatory support. *C. botulinum* was cultured from wounds in 14 of 19 patients (74%). Toxin was identified in the serum of six patients (the case reported from Tennessee had toxin shown in the tissue surrounding the wound, but not in the serum). The type of toxin or organism was type A in 12 cases, type B in 5 cases, types A and B in 1 case and was not typed in 1 case (Wyoming, 1986). The mean time between injury and the onset of symptoms was ten days. Most of the cases (12 of 19 or 63%) were associated with compound fractures or crush injuries, two cases were associated with puncture wounds and two cases were associated with skin lesions resulting from IV drug abuse. There was one case following a cesarean section, one following a dirty laceration of the left leg and one associated with a laceration of the plantar aspect of the right foot from stepping on a piece of glass (A.T. Pavia, MD, oral communication, January 1987).[1]

In addition to the two confirmed cases of wound botulism associated with IV drug abuse (1982[3] and 1984), two additional cases of botulism from unknown sources have been reported in IV drug abusers. Both of these cases had botulism toxin in their serum, but no source could be found. These cases probably represent wound botulism from clinically inapparent foci of *C botulinum*.[1] From 1982 through 1983, four additional cases clinically suggestive of botulism (cranial nerve dysfunction followed by symmetric descending paralysis) in persons who abuse drugs were reported although not confirmed through culture or demonstration of botulism toxin.[4]

In the case presented herein, cranial nerve dysfunction developed seven to ten days after the patient had a puncture wound to his right heel. This was followed by symmetric descending paralysis requiring complete ventilatory support for more than 30 days. His clinical symptoms were compatible with the paralytic condition caused by neurotoxins elaborated by *C botulinum*. The laboratory diagnosis of botulism was confirmed by identifying the botulism toxin in the patient's serum (mouse toxin neutralization assays). The type of botulism toxin (type A or type B) could not be determined because of an insufficient quantity of serum. Although the mouse toxin neutralization assay is a specific test for showing botulism toxin, it has not been a particularly sensitive test. Of the 19 patients since 1976 reported to have wound botulism, only 6 (32%) had botulism toxin shown in their serum specimens.[1] It appears that botulism toxin is more likely to be detected in a patient's serum when the test is done closer to the onset of clinical symptoms.[5]

In the case presented, *C botulinum* organisms were not isolated from the wound or identified by fluorescent antibody testing of the retained foreign body (wood splinter). The puncture wound, however, with its retained foreign body, was the only evident source of his botulism. *C botulinum* may not have been identified in the wound specimen because the patient had been given antibiotics (dicloxacillin, penicillin) to which *C botulinum* is generally sensitive or because the specimens for anaerobic culture may not have been handled properly. Because of the patient's history of IV drug abuse (cocaine one month before admission), his skin was examined thoroughly for lesions, particularly at the site of previous subcutaneous or intravenous drug administration. No skin lesions were identified.

Electrophysiologic studies are helpful and, when done, have suggested the diagnosis of botulism in most patients, especially when repeated at intervals during the clinical course.[2,6] The electrical abnormalities in cases of botulism, however, evolve over time and may not be present early in the disease.[6] Electrophysiologic studies indicate a decreased amplitude of the evoked muscle action potential to a single supramaximal nerve stimulus in acute polyneuropathy, myasthenia gravis and botulism. In botulism and the Eaton-Lambert syndrome, however, repetitive stimuli (25 to 50 per second) produce potentiation with an incremental increase in the muscle-potential amplitude. This incremental increase may not be evident in all limbs and is not as great as in the Eaton-Lambert syndrome, especially in severe cases of botulism.[6-8] The degree of potentiation appears to be related to the ability of a nerve terminal to release acetylcholine after rapid nerve stimulation and may be less pronounced in more severe cases of botulism where the neuromuscular block is greater.[6]

The early diagnosis of botulism in isolated cases may be difficult. The initial cranial nerve dysfunction may be misdiagnosed (as pharyngitis or effects of drug abuse, for example) and later the symmetric descending weakness must be differentiated from acute polyneuropathy (an atypical descending variant of the Guillain-Barré syndrome) and from myasthenia gravis. Acute polyneuropathy generally produces a loss of deep tendon reflexes at the peak of the illness and an elevation of the cerebrospinal fluid protein level. The protein concentration in cerebrospinal fluid does not always increase, however, and is frequently not evident for three to six weeks after the onset of clinical symptoms.[9] Usually the Guillain-Barré syndrome is a symmetric paralysis that begins peripherally and ascends. Occasionally (in less than 5%) it may begin as ophthalmoplegia and descend (ophthalmoplegia, ataxia and areflexia—the Miller Fisher syndrome).[9] Myasthenia gravis is typically diagnosed by a dramatic resolution of the paresis in response to administering acetylcholinesterase inhibitors (edrophonium). The use of edrophonium usually does not ameliorate the paresis or paralysis associated with botulism toxin, though some improvement has been reported in milder cases.[6] In 85% to 90% of cases with generalized myasthenia gravis, acetylcholine receptor binding or blocking antibodies are identified in the patient's serum.[10]

Once a diagnosis of wound botulism has been made, surgical debridement of the wound and intensive respiratory care are the most important aspects of therapy.[2,8] The appearance of the wound may not be clinically helpful. In the series reviewed by Hikes and Manoli,[2] traumatic wounds in 8 of 13 cases (where information was available) were considered clean at the time symptoms of botulism occurred. In patients who abused drugs, two of four cases of confirmed botulism reviewed by MacDonald and colleagues did not have obvious wounds or sites of infection when the patient presented.[1,4]

The efficacy of the use of botulism antitoxin in the treat-

*The fluorescent antibody testing was done by Charles L. Hatheway, PhD, Chief of Botulism Laboratory and Enteric Bacteriology Section, Division of Bacterial Diseases, Center for Infectious Diseases, CDC.

ment of wound botulism has not been firmly established,[8] probably because of the small number of cases and a delay in diagnosis and the administration of antitoxin. Antitoxin has been reported to improve the outcome in cases of type E food-borne botulism,[11,12] though wound botulism associated with type E toxin has not been reported (wound botulism has been associated only with type A or type B toxin or both).[8] Tacket and co-workers, however, have reviewed the effect of antitoxin therapy on outcomes in 132 cases of type A food-borne botulism occurring between 1973 and 1980.[13] They found that those patients who received antitoxin within 24 hours after the onset of symptoms had a shorter clinical course and a lower fatality rate than those who did not receive antitoxin. Furthermore, patients who received antitoxin more than 24 hours after the onset of symptoms still had a lower fatality rate than those who did not receive antitoxin, though their clinical course was not significantly shortened.[13] Because botulism toxin binds tightly ("irreversibly") to the presynaptic membrane of the neuromuscular junction (inhibiting the release of acetylcholine), early administration of antitoxin may decrease the amount of toxin bound to the presynaptic membrane. As long as botulism toxin is present in a patient's serum, antitoxin may be beneficial and should be given. The use of botulism antitoxin is associated with a 9% incidence of hypersensitivity reactions (5.3% acute and 3.7% delayed).[14] In a review of 268 persons given botulism antitoxin of equine origin during an 11-year period (1967-1977), 24 (9%) had nonfatal hypersensitivity reactions to a skin test or a therapeutic dose of antitoxin. Reactions were anaphylactic in about 2%, immediate hypersensitivity (rash or urticaria) occurred in about 3% and serum sickness in about 4% of patients.[14]

Antibiotics have not been shown to be efficacious in treating or preventing wound botulism.[2] Certainly, in the case presented, antibiotic treatment of the cellulitis did not prevent the development of botulism. Because patients in whom wound botulism develops are often receiving antibiotics at the time signs and symptoms of botulism occur, and because it is known that polymicrobial infections tend to inhibit clostridia, it has been suggested that antibiotic treatment may even enhance the growth of *C botulinum* by changing the bacterial milieu (eliminating more sensitive organisms) in the wound.[2] An alternate explanation is that antibiotics may not adequately penetrate into the wounds, which are sufficiently avascular to provide suitable conditions for the growth of *C botulinum*.[15]

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Overuse of Health Resources by Penicillin-Sensitive Children

To the Editor: Regarding the article "Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior Penicillin Sensitivity" in the June 1987 issue,[1] I agree with the authors that allegedly penicillin-sensitive children utilize medical care and antibiotics at a greater rate than other children. But I believe that a possible explanation has been overlooked.

I propose the following: Such children have a higher rate of utilization *before* being labeled as penicillin-sensitive and are more frequently prescribed antibiotics. That is, because they are taken more frequently to physicians, possibly by parents who are more demanding that "something be done," they might more often be given penicillin and its derivatives for exanthem-producing illnesses or gastroenteritides likely to provoke a "reaction." The fact that they are thereafter found to relatively overutilize health resources is merely a continuation and possibly an exacerbation of previously inappropriate behavior on the part of parent and physician alike.

While undoubtedly as guilty as everyone else of inappropriate prescribing of antibiotics, I believe this possible explanation of the observed phenomenon is worthy of investigation.

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Two Articles in WJM

To the Editor: As usual, there are two articles in the May 1987 issue that have thoroughly gripped my attention. Not as usual, however, they have left me feeling sad and frustrated rather than educated and uplifted.

John La Puma, MD, describes 27 case consultations in clinical ethics at the University of Chicago from July 1985 to June 1986.[1] As he states, "The referred cases involved a broad range of issues, most of which focused on questions of foregoing one or more life-sustaining therapies in seriously ill patients." Specifically, eight cases involved DNR orders or the limits of care in patients with terminal cancer. Several more cases addressed these same issues in patients with severe, chronic illnesses other than cancer.

What saddens me about this article is not the results. Dr La Puma and his colleagues followed an exemplary format and did thoughtful and caring consultations. What saddens me is the fact that some of these cases required an ethics consultation at all.

Ethics consults can be extremely valuable, both clinically and educationally; indeed, some of the cases presented by La Puma ask hard questions that beg an ethicist's opinion. Still, I cannot help but feel that others of these 27 cases would not have required formal ethics consults if a primary care physician had been involved. Patients with cancer and other chronic illnesses do not deteriorate and die unexpectedly. There ought to be ample time to discuss resuscitation and the limits of care with them and their families well in advance. Such discussions are not routine, however, as Dr La Puma notes: "Busy physicians, even those with an interest in ethics, may tend to marginalize patients' personal values and histories, with these data falling to the side, especially when a patient is critically ill." How sad.

The second article is the editorial on the future of primary care in which the editor calls for more and better research into this discipline. "Discipline?" I wish I knew what discipline it is that you would like to research because I, too, am often frustrated by the lack of recognition given my specialty (family practice) by those who find it too "un-academic."

Unfortunately, I do not think that primary care is a discipline. It is an attitude—an approach, a way of doing medicine—and such things are difficult to research. The combination of scientific, educational and pastoral qualities that create good primary care medicine is not easily studied. When it is, such studies are called "soft" and easily dismissed.

Furthermore, I'm not sure that research into the doctor-patient relationship is the answer. Not that it won't help, but the goal of research is to establish facts—facts which can then be taught and used for future work. How does teaching facts about attitudes make the attitudes themselves useful? Primary care facts may help communicate the existence of primary care attitudes but how will they instill them in physicians? Such research reminds me of the various proofs that God exists.

Values and attitudes—for myself at least—are learned only with difficulty and are not easily taught. Appreciation for the art of patient care may well be enhanced by further investigation of the doctor-patient relationship, general systems theory and models of health education. Art appreciation and art performance, however, are not the same.

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2. Watts MSM: Primary care—Does it have a future? (Editorial). West J Med 1987 May; 146:613

Primary Care—Does It Have a Future?

To the Editor: In regards to your editorial in the May issue, "Primary Care—Does It Have a Future?,"[1] after 30 years as a general practitioner, I often wonder the same. I am uncertain how to advise students today as to choice of field. Medical educators, if they have any brains, should promote a large body of "family practitioners" and general internists, lest the subspecialists and superspecialists have their time diverted by trivia or common problems

There is no perfect answer. As you alluded to, however, human interaction can still exist in the specialties. I certainly see a lot of specialists who catch on quickly to family dynamics and emotions of their patients.

I don't *want* to be a gatekeeper for the insurance companies (the trend)—it is demeaning, time-consuming at no pay

and disappointing when the insurance plan has a pitiful number of hungry, second-rate specialists to refer to.

Keep writing—I've always admired your work.

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REFERENCE

1. Watts MSM: Primary care—Does it have a future? (Editorial). West J Med 1987; 146:613

Where Is the Pathologist?

TO THE EDITOR: The editorial by Helen Ranney, MD, in the April 1987 issue[1] seems to support the thesis that the data generated by electronic hematologic counters make examination of the peripheral blood smear less necessary, and when morphologic examination might be required, a medical technologist could best perform this function. A glaring omission in the process is the role of the pathologist. In most hospitals, smears generated from electronic counter abnormalities using preset criteria are reviewed by the pathologist. This is really the vital link between the laboratory and the clinician, assuring that significant data do not become "lost" in the ever-growing laboratory section of the chart.

Although electronic counters are excellent screening tools that are continuing to revolutionize the field, they have limitations and many abnormalities need confirmation by blood smear examination. The hematologists who practice at our institution never fail to stop off in the laboratory to review the smear before visiting their patients.

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REFERENCE

1. Ranney HM: Clinical evaluation of anemia (Editorial). West J Med 1987 Apr; 146:473-474

* * *

Dr Ranney Responds

TO THE EDITOR: I apologize for the incorrect reference given in my editorial, "Clinical Evaluation of Anemia."[1] The first reference should have been the study by Jen and co-workers.[2] In that study, examination of the blood smear was "no better than the red blood cell indices in detecting probable iron deficiency or low serum levels of folate or vitamin B_{12}. In anemias not caused by deficiency states, the blood smear reading performed by the hospital laboratory provided unique information in 6 percent of the cases and helpful information in another 25 percent. But the additional reading performed by a hematologist never provided unique information and provided incremental helpful information in only 4 percent of the cases." The authors conclude that, in their hospital, "a routine personal reading by a physician had limited incremental value and could be reserved for selected cases," notably, the confirmation of platelet counts and evaluation of abnormal leukocyte counts or leukocyte morphology. Most physicians would agree with those authors that physicians should review the blood smears in selected cases, such as in severe cases of hemolytic anemia, anemia of uncertain cause even after evaluation, anemia in which a patient unexpectedly fails to respond to treatment or anemia associated with abnormal white cells either in number or morphology. Because these patients are frequently referred to hematologists, many internists leave the slide review to the hematological consultant.

In many teaching hospitals there are one or two senior, often supervising, medical technologists who have developed great proficiency in analyzing blood smears. Perhaps such technologists were involved in the study cited. Such respected names in American hematology as Geneva Daland, who was associated with W.B. Castle, MD, and coauthored a book with him, and Virginia Minnich, who worked for many years with Carl Moore, MD, are examples of medical technologists whose skills in smear interpretation were greater than the skills of many hematologists. Technologists with such skills provide excellence to a laboratory. Like Dr Bark, I think that most hematologists continue to examine blood smears. The cost of laboratory work might be reduced, however, by allowing the referring physician to designate the desired reviewer of the smear, that is, a hematologist or pathologist would review only on specific request.

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Wright's Law Is Right on

TO THE EDITOR: Bravo! And thank you for publishing the absolutely brilliant "Wright's Law" in the June 1987 issue.[1] Wright is right. Economics writes history (contemporary US medical history, that is). Right on, Wright.

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Insects in the Operating Room

TO THE EDITOR: Reports of insects in the operating room, while not common, have been described in patients with poor hygiene and who have not showered prior to their same-day operation.[1] When dealing with the ubiquitous insect world, it must be remembered that one's personal hygienic habits do not necessarily protect against bringing insects into the operating room.

A case in point is that of a 30-year-old man who was brought to the University of California, Davis, Medical Center—a major trauma center for northern California—after being involved in a serious roll-over motor vehicle accident; apparently paramedics found him lying in a field off the side of the road. Several hours into the surgical debridement and repair of the patient's open right humeral fracture and brachial artery laceration, an insect was noted crawling out from under the sterile drapes, towards the wound. The trespasser was arrested by the surgical technique known as "squashing," and was sent to the pathology department for identification.

Fortunately, the beak, one antenna and half of a wing were intact enough to identify the roaming creature as a Hemiptera ("true bug"), probably a damsel bug, belonging to the family Nabidae, genus *Abis*. This bug has the same general shape, although smaller size, as the dreaded kissing and assassin bugs. The damsel bug is a common predator of small insects, such as aphids and caterpillars and is often found in grassland areas. The patient undoubtedly acquired this inadvertent hijacker during their forced cohabitation of the roadside field.

Several important lessons are revealed by this case. First, despite thorough physician prepping and hygienic efforts for the patient, completely sterile conditions are not always achievable in the operating room, especially when dealing with trauma or emergency operations. Fortunately, with the use of prophylactic antibiotics, this insect probably transmitted no infection, despite the millions of bacteria, belonging to hundreds of species, which have been found to cover a single insect.[2]

Finally, it is well recognized that few of even the most common insects seen by laypersons are identified correctly. Without the necessary appendages, the insect in this case may not have been distinguishable from other more serious pests. Therefore, it is valuable to save for proper identification any questionable arthropod, just as one would send for histologic confirmation most "probably benign" subcutaneous nodules. If an arthropod is to be identified, make sure it is reasonably intact; even the most experienced entomologists have difficulty when presented with disarticulated "bugs," or mere remnants thereof.

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Asthma and Urticaria After Hepatitis B Vaccination

To the Editor: In accordance with the recommendation of the Centers for Disease Control,[1] 20 μg of plasma-derived hepatitis B vaccine (Heptavax-B, lot 2445H) was administered to a serosusceptible 31-year-old employee in a high-risk occupation. Within 30 minutes generalized pruritus, dyspnea, urticaria and infraorbital edema developed. Extensive expiratory rhonchi were present in both lungs. She was given 0.3 ml epinephrine 1:1,000 dilution subcutaneously. Her symptoms only partially resolved, and the same dose of epinephrine had to be repeated four hours later. She was prescribed diphenhydramine hydrochloride, 25 mg as needed, and hydroxyzine hydrochloride, 25 mg at bedtime. This led to significant relief the next day. The patient had a leukocyte count of 8,500 per μl with 12% eosinophils and a raised total serum immunoglobulin E level. On questioning, she revealed that she had experienced a similar but less severe reaction to the vaccine's first dose four weeks earlier, when dyspnea and generalized itching developed, which were relieved by an injection of diphenhydramine by her personal physician. She had totally forgotten the link between the vaccine and the reaction. She said she did not have other allergen exposures such as bee sting, new perfume, new clothes, chemical exposures or the like.

The patient has not been given the third dose of vaccine. She has remained negative for hepatitis B surface antibody and has not acquired the hepatitis B core antibody or hepatitis B surface antigen while continuing in her employment. She had a history of bronchial asthma and allergy to sulfonamides but no history of atopic dermatitis, allergic rhinitis or urticaria. She had been asymptomatic for several days before both vaccine doses.

Heptavax-B contains inactivated hepatitis B surface antigen, an alum adjuvant and thimerosal, a preservative. Based on a literature review, thimerosal was considered to be the inciting allergen in this case. Thimerosal has produced ocular allergy through contact lens solution[2] and eye cream[3] as well as cutaneous and system allergy.[4-6] Caution should be exercised in administering Heptavax-B to persons allergic to other vaccines or medicines containing thimerosal. Thimerosal is also present in the yeast-derived hepatitis B vaccine (Recombivax-HB).

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Topics in Primary Care Medicine

Reflex Sympathetic Dystrophy Syndrome

Diagnosis and Management

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Reflex sympathetic dystrophy syndrome (RSDS) is a symptom complex characterized by diffuse pain and swelling in an arm or leg distally, coupled with vasodilation or vasoconstriction and trophic skin changes. Additional features of the syndrome may include limitation of shoulder motion (frozen shoulder), flexion deformities of fingers, muscle wasting or alteration in sweating and bilateral involvement. Earlier descriptive terms applied to this disorder include shoulder-hand syndrome, causalgia, Sudeck's atrophy, traumatic angiospasm and posttraumatic osteoporosis.

The aim of this review is to highlight the clinical features and precipitants of RSDS, discuss the diagnostic approach and outline therapeutic modalities. Heightened awareness of the clinical spectrum, knowledge of the wide array of predisposing events or triggers and prompt institution of therapy are needed to prevent protracted cases with persistent limitation of function.

The pathogenesis of RSDS has to a great extent remained obscure. Any hypothesis must account for several features: the precipitation of RSDS by many unrelated events; the clinical involvement of many anatomic structures, including skin, blood vessels, synovium and bone; a variable spectrum of clinical disease, often with a long duration, and the apparent response of RSDS to sympathetic blockade. Most hypotheses invoke an event (such as trauma or stroke) triggering an abnormal central reflex arc, leading to accentuated autonomic outflow that results in the clinical manifestations of RSDS.

Clinical Features

The precise incidence of RSDS in adults is unknown, but several retrospective studies have been done. In one, RSDS developed in a hand or foot of approximately 0.01% of patients with crush injuries, fractures or dislocations. In another series, 3% of postoperative patients had RSDS after surgical treatment of an arm or hand. Also, several studies suggest that RSDS can develop in as many as 10% of patients with strokes.

RSDS has been reported in adults, adolescents and children. The usual interval between the putative precipitating event and the onset of symptoms is several weeks, although an interval as short as one day or as long as several years has been noted. The causal association is less clear when several years have elapsed.

Triggering Events

No prospective studies evaluating the causal associations of various pathologic conditions and RSDS have been done, but in several large retrospective series trauma, surgical procedures, neurologic disorders and medical conditions were reported to possibly trigger the syndrome (Table 1). Trauma is the most common precipitant, accounting for 30% of cases. While wrist and hand fractures most frequently trigger the syndrome, crushing injuries, lacerations, sprains, burns, bruises or penetrating wounds may also antedate the onset of symptoms. In addition, trauma of the spinal cord, shoulder, neck, arm or lower extremity has been associated with RSDS. The syndrome can follow a variety of surgical procedures, including carpal tunnel decompression, Dupuytren's contracture repair or ganglion excision. It has also been observed after an open-heart operation, thoracotomy and hip or lower extremity procedures.

Neurologic disease accounts for about 20% of cases. Strokes and peripheral nerve entrapment or injury (median, ulnar nerve or branchial plexus) are the most common precipitating neurologic events. Other neurologic causes include neoplasm, subarachnoid hemorrhage, head injury and spinal cord lesions. There are also several reports of RSDS associated with herpes zoster infections.

Finally, there are numerous anecdotal reports of RSDS occurring after myocardial infarctions and in association with cervical spondylosis, and some case reports associate it with internal malignant disorders, metabolic bone disease and drugs, such as barbiturates and antituberculous agents. Despite a thorough evaluation, 10% of all patients with RSDS have no identifiable precipitant.

(Smith DL, Campbell SM: Reflex sympathetic dystrophy syndrome—Diagnosis and management. West J Med 1987 Sep; 147:342-345)

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Clinical Manifestations

The cardinal manifestations of RSDS are distal pain, swelling and vasomotor disturbances (Table 2). Other findings include dystrophic skin and nail changes and limitation in finger motion. RSDS is usually unilateral but in 10% to 20% of cases it can be bilateral. Most clinical descriptions involve the arm, but leg involvement may occur. The frozen shoulder syndrome, or adhesive capsulitis, commonly accompanies RSDS and may be a variant of it.

RSDS is variable in presentation and changes with time. The clinical features have been divided into three stages, though these stages may not always be distinct.

Stage 1. This stage ordinarily lasts several weeks to six months. A gradual or abrupt onset of a painful, stiff shoulder is accompanied by diffuse swelling, pain and stiffness in hand and fingers. The pain is characteristically intense and burning and is not limited to a specific dermatome. It may be exacerbated by exposure to cold. On examination, the hand is diffusely tender, edematous and dusky, red or pale in color or may have a mottled appearance. The skin is smooth and sweaty. The hand is frequently held in a guarded and flexed position.

Stage 2. This stage usually lasts three to six months and is characterized by gradual resolution of the shoulder pain, but shoulder, wrist and hand stiffness remains. Burning, diffuse hand, wrist or forearm pain persists. Periarticular tenderness at the wrist or the metacarpophalangeal joints is frequently present. Wasting of intrinsic hand muscles and subcutaneous tissues, flexion deformities of fingers and hand-grip weakness become more pronounced. The hand is cool and the color blanched, grey or cyanotic. Dystrophic changes develop in the skin with loss of hair, and the palmar fascia may be thickened. Nails appear dystrophic, cracked or brittle.

Stage 3. This stage lasts several months or may become chronic and irreversible. There is progressive notable limitation of motion in the small joints of the hand, associated with pronounced wasting of intrinsic muscles and subcutaneous tissues. Contractures resembling Dupuytren's contracture frequently are present. The skin is atrophic and smooth, glossy or glazed in appearance. The distal extremity is cool and pale. The shoulder is frequently partially or completely immobile. The pain may spread proximally.

TABLE 1.—*Precipitating Events or Conditions Associated With the Reflex Sympathetic Dystrophy Syndrome*

Trauma	Neurologic
Wrist/hand fracture	Cerebrovascular accident
Ankle/foot fracture	Peripheral nerve entrapment or injury
Crush Injury	Head trauma
Contusion	
Sprain	Intrathoracic
Laceration	Myocardial infarction
Spinal cord injury	Thoracic or cardiac surgery
Electrical or thermal burn	Infection
Postoperative	Other
Carpal tunnel decompression	Neoplasm
Dupuytren's contracture repair	Cervical osteoarthritis
Ganglion excision	Herpes zoster
Hip or knee surgery	Metabolic bone disease

Clinical Course

While RSDS was initially thought to always be self-limited, more recent evidence suggests that a chronic course may be common. In general, clinical experience indicates that the prognosis may be improved when the condition is recognized in stage 1 or early in stage 2 and therapy is immediately begun. When the diagnosis is established during the later part of stage 2, the chance for complete recovery is less likely. Although symptoms may become less severe, persistent pain, stiffness, joint contractures and a degree of atrophy may continue in 20% of cases. The severity or nature of the precipitating event does not appear to influence either the development of the syndrome or the clinical outcome. In stage 3, the findings of joint contractures and muscle and skin atrophy may simulate those of sclerodactyly, and an intractable pattern commonly is established despite intensive therapy.

Diagnostic Methods

The variability in presentation and course of the reflex sympathetic dystrophy syndrome has prevented the development of a uniform definition. In our view, the most useful criteria are those listed in Table 3 (adapted from Kozin and associates). Radiographic and scintigraphic studies are useful in supporting the diagnosis in patients suspected of having RSDS. Osteopenia—the result of continuous hyperemia or other local factors—is the most common radiographic abnormality and is seen in 70% of patients with RSDS. Detectable osteopenia rarely occurs before the sixth week of symptoms, however. When present, there is either patchy local or diffuse demineralization in the affected extremity. "Crumbling" erosions of subchondral or juxtaarticular bone or the small joints of the hands and feet or wrist and ankle may also occur. Histologic examination of synovium shows only moderate proliferation and disarray of synovial lining cells associated with small blood vessel proliferation and edema.

Bone scans using methylene diphosphonate labeled with technetium Tc 99m in patients with RSDS often show increased blood flow and regional pooling, even if an x-ray film is normal. Delayed images taken several hours after intrave-

TABLE 2.—*Clinical Findings in the Reflex Sympathetic Dystrophy Syndrome**

Clinical Finding	*Percent With Finding (Range)*
Pain	
Distal pain	98 (96-100)†
Tenderness	72 (55-88)†
Hyperesthesia	79 (69-88)†
Swelling	62 (46-69)†
Vasomotor changes	
Erythema	47 (36-60)†
Cyanosis	8 (5-16)
Warmth	15 (6-21)†
Raynaud's phenomenon	12 (2-20)
Dystrophic changes	
Hypertrichosis, nail changes, atrophy	47 (21-60)
Hyperhydrosis	32 (21-40)†
Decreased hand/finger movement	77 (37-88)†
Bilateral (clinical findings)	22 (10-25)

*Table represents compilation of four studies encompassing 714 patients. Not all findings were noted in each study. Patients at all stages of disease were described. Those changes usually seen in early disease are marked with a dagger (†).

nous injection almost invariably show diffusely increased juxtaarticular uptake in multiple joints in an affected extremity. This presumably represents increased periarticular blood flow and bone turnover. In the diagnosis of RSDS, these scans have a variable sensitivity (60% to 90%) but high specificity (92% to 98% [based on clinical criteria]). Although an abnormal scan may confirm the clinical diagnosis in possible or definite cases, its diagnostic value in uncertain cases is not established. In addition, preliminary data suggest that patients who have an abnormal radionuclide scan appear to have the best chance for a therapeutic response.

When there is an obvious preceding trigger and classic features of RSDS are present, there is little difficulty in establishing a clinical diagnosis. Confusion may arise, however, if the manifestations are subtle or atypical, if no trigger is uncovered or if there is a long time interval between the initial insult and the onset of symptoms. Under these circumstances, other conditions should be considered in the differential diagnosis. These include Raynaud's disease, neurologic or neurovascular entrapment or compression syndromes—such as carpal tunnel syndrome, thoracic outlet syndrome—early scleroderma, mixed connective tissue disease, hypertrophic osteoarthropathy or vascular insufficiency.

Therapy for RSDS

RSDS may follow a benign course, causing few symptoms and resolving without therapy; conversely, it may last for years, leading to chronic pain and disability. The decision to institute therapy for the syndrome is at best a matter of clinical judgment. The overall management of RSDS is controversial, due in large part to difficulties in diagnosis and variability in disease expression and course. Given the paucity of controlled trials, it is not known if early therapy alters the natural history of mild disease, but there is agreement that therapy is most effective when initiated within the first several months of onset in severe cases.

RSDS following trauma or a surgical procedure may be preventable by early mobilization of the involved extremity. Physical therapy in various guises has been used in the management of the disorder, although its value has not also been confirmed in controlled clinical studies. There may be some theoretic disadvantages to further stimulating the autonomic nervous system by the vigorous use of heat or cold, or by forcefully manipulating an already painful extremity. On the other hand, the judicious use of range-of-motion exercises and splinting to prevent deformity in the early stages, and of rehabilitation in the later phases of the syndrome, can be of great value.

Most recent studies of the treatment of RSDS have focused on two interventions: sympathetic blockade and corticosteroid therapy.

Sympathetic Blockade

Sympathetic blockade presumably inhibits the abnormal vicious cycle of sensory afferent-sympathetic efferent discharge that may lead to RSDS. Several forms of sympathetic blockade have been analyzed in uncontrolled studies.

Local sympathetic blockade. Infusing guanethidine sulfate or reserpine into an extremity can disrupt local or ganglionic transmission of sympathetic impulses. An infusion can be given intra-arterially or intravenously into a transiently exsanguinated limb (analogous to a Bier block for anesthesia). This therapy is well tolerated, and many patients are given at least transient benefit. This therapy is limited to research settings.

Regional sympathetic blockade. The stellate ganglion, supplying the major sympathetic innervation to the arm, lies in the lower cervical prevertebral fascia. Percutaneous infiltration with long-acting local anesthetics results in stellate ganglion blockade, manifested by a unilateral Horner's syndrome and a cool extremity, and may result in rapid pain relief in many patients. Although this effect is frequently only temporary, repeated blockade (four to seven times) or continuous infusion of anesthetic for several days through an indwelling catheter can result in prolonged or permanent benefit. Similar methods can be applied to patients with RSDS of a lower extremity, although the technique is more difficult.

Surgical sympathectomy. Surgical removal of the paravertebral sympathetic ganglia serving an extremity interrupts sympathetic flow and may ameliorate the symptoms of RSDS. Surgical sympathectomy appears to be indicated in those patients benefiting (albeit transiently) from repeated regional sympathetic blockade. The lack of benefit from regional blockade argues against the use of surgical sympathectomy. Complete removal of sympathetic outflow to an arm via a thoracotomy and pleural incision is probably the best procedure. Most studies suggest a 75% improvement rate with surgical sympathectomy.

Corticosteroids

Systemic administration of corticosteroids has been used empirically for years in patients with RSDS. The mechanism of action is unknown, particularly because there is evidence for only mild inflammation, if any, in RSDS. Two recent studies have supported the efficacy of corticosteroids. In a randomized, controlled, blind study, Christensen and coworkers treated 23 patients with either prednisone, 10 mg given orally three times a day, or placebo for as long as 12

TABLE 3.—*Diagnostic Clinical Features and Supportive Criteria for the Reflex Sympathetic Dystrophy Syndrome (RSDS)*

Definite RSDS
Pain, swelling and tenderness in an extremity
Symptoms and signs of vasoconstriction or vasodilation
Dystrophic skin or nail changes usually present
Probable RSDS
Pain and tenderness in an extremity and *either*
Symptoms and signs of vasoconstriction or vasodilation *or*
Swelling
Dystrophic skin or nail changes often are present
Possible RSDS
Symptoms or signs of vasoconstriction or vasodilation and *either*
Swelling *or*
Tenderness
Dystrophic skin or nail changes are occasionally present
Doubtful RSDS
Unexplained pain and tenderness in an extremity without history or evidence of vasoconstriction or vasodilation
Dystrophic skin or nail changes are not present
Supportive Criteria
Abnormal delayed-image radionuclide bone scan showing increased periarticular activity in several joints
Radiographs of the affected distal extremity show localized patchy osteopenia

weeks; all 13 patients given prednisone had pronounced improvement in pain and swelling, while only 2 of 10 given a placebo had similar improvement. In an uncontrolled series, Kozin and colleagues used a higher dose of oral prednisone, 40 to 60 mg per day, initially, with a rapid decrease over two to four weeks; 70% to 80% of patients had a good to excellent response. Patients treated in the early stages of the disease and patients with abnormal bone scans responded more often. In this study, corticosteroids given systemically were much more effective than regional ganglionic blockade.

Many other modes of therapy have been proposed, including transcutaneous nerve stimulation, acupuncture and drugs—that is, β- and calcium channel-blockers and calcitonin—but reports are sparse and anecdotal. Their role in the treatment of RSDS remains unclear.

In summary, the therapy for RSDS is likely to be most successful when instituted early. Some patients with early RSDS may, however, have spontaneous resolution of their disease. Attempts to prevent the syndrome with early limb mobilization after trauma seem reasonable. Established disease, especially when coupled with a positive bone scan, may respond to systemic corticosteroid therapy. Regional or local sympathetic blockade may help some patients, although the benefit can be transient. The comparative benefits of regional or surgical sympathectomy versus corticosteroids given systemically are still unresolved; risk and cost considerations would seem to favor the use of corticosteroids.

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The Medical Pros and Cons of The Pill

LET US SUPPOSE that 10 million women in the United States take oral contraceptives in 1987, which is about the same number that took them in 1986. If that proves to be the case, then 1,070 women will have a heart attack or stroke because they take birth control pills, but 1,700 women will not have ovarian cancer because they take birth control pills. Benign tumors of the liver will develop in 300 women, but 2,000 women will not have endometrial cancer. Gallstones will develop in 860 women, but 3,500 women will not have ovarian retension cysts. Venous vascular disease will develop in roughly 7,200 women because they take birth control pills, but 11,500 women will not have ectopic pregnancies, 15,500 women will not have acute salpingitis and 23,500 women will not have benign breast disease because they take birth control pills.

—BARRY E. SCHWARZ, MD

Extracted from *Audio-Digest Obstetrics & Gynecology*, Vol. 34, No. 8, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Seminars in Health Care Delivery

How Physicians Can Improve Patients' Participation and Maintenance in Self-Care

LAWRENCE W. GREEN, DrPH, *Houston*

This feature will appear regularly in The Western Journal of Medicine. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

A protocol for the stepped education and support of patients is derived from the cumulative experience of more than 200 clinical trials of patient education and behavioral change interventions. The recommended procedure entails assessing a patient's educational needs by asking a sequence of "diagnostic" questions to assure patient motivation, skill and resources and to reinforce adherence to the prescribed medical regimen or life-style modifications. The sequence of questions and interventions is also designed to minimize a physician's time commitment and to maximize the medical benefit to the patient.

(Green LW: How physicians can improve patients' participation and maintenance in self-care. West J Med 1987 Sep; 147:346-349)

All too often physicians arrive at a correct diagnosis and devise appropriate management plans, only to be frustrated by unsatisfactory outcomes resulting from the patient's not understanding instructions or, in many instances, choosing to ignore them. What sustains an outpatient's adherence to a prescribed medical regimen between visits? The answer, apparently, is that not enough sustains their behavior. A physician sees countless indicators of instructions and admonitions gone astray. Patient adherence failure, often called noncompliance, is reflected most clearly in relapse rates ranging from 20% to 80%, not only in nonadherence to medications, but even more in ignoring advice on life-style modifications.[1] We estimated from reviews of patient education studies and epidemiologic models that more effective physician interaction with a patient's teaching could reduce drug errors and improve clinical outcomes by as much as 40% over conventional treatment.[2]

The Curve for Adherence Relapse

The curve shown in Figure 1 is typical of the relapse pattern in a variety of practices recommended to patients, especially those practices relating to addiction, compulsive behavior, pleasures, comforts, unpleasant side effects, inconvenience, costs or even simple habits. Assuming that 100% of the patients who leave a physician's office are committed to adopting the prescribed practice, there is a characteristic drop of 40% to 80% in actual maintenance behavior during the first six weeks.[3]

Though the shape of the curve is highly predictable, the drop in percentage before it levels off is not. More effective intervention by physicians for selected self-care practices can alter the curve's slope and plateau levels.[4] For example, physicians can reduce a male patient's daily consumption of cigarettes by simply giving advice, as shown in a randomized clinical trial that also documented lower mortality in lung cancer compared with the control group.[5] In our long-term follow-up of Johns Hopkins ambulatory patients in a randomized controlled trial using health education for hypertension, we found sustained improvement in blood pressure control and more than 50% fewer deaths in those who had received some combination of patient education than in the controls.[6] In a family planning clinic, women smoked less when they were exposed to a combination of a physician's advice and waiting room media than when they were exposed only to waiting room media.[7]

A more positive way of interpreting the relapse curve is to note that as much as 40% to 60% of the population does maintain its self-care practices. This fact indicates that any global intervention program designed to prevent relapse may be unnecessary and probably wasteful for a large portion of patients entering health care programs. Furthermore, the interventions designed to prevent relapse range from simplistic, inexpensive methods effective for only a few patients to complex, obtrusive and costly methods effective for most but needed by few.

Characteristics of Patients Who Do Not Adhere to Self-Care Programs

Given these descriptions of the problem, considerable study has been devoted to identifying the characteristics of

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patients or participants in medical care and health programs who typically drop out or fail to sustain the recommended behavioral changes. Comparative and prospective studies have identified four sets of correlates that predict adherence or relapse: (1) demographic and socioeconomic characteristics; (2) motivational characteristics; (3) physical, manual or economic facilitators and barriers, and (4) circumstantial rewards and penalties associated with the behavior, especially in the social environment.

The first of the four sets of factors—demographic and socioeconomic characteristics—cannot be easily changed, especially in the clinical setting; the other three sets of factors can. The second is easier to change than the third, and the third easier than the fourth. This hierarchy of factors influencing adherence and relapse suggests a logical order of intervention that should maximize the impact on a patient while conserving the energy and time of the physician. The logic, as in that applied in stepped care, would dictate the concentration of educational resources on patients according to which of the three changeable characteristics they possess.[8] It would further dictate that if a patient possesses more than one of the changeable characteristics predicting relapse, a combination of interventions designed to change the characteristics should be applied.[9]

A Hierarchy of Adherence Factors

One additional fact about the three sets of changeable characteristics predicting adherence or relapse is that they reflect a natural hierarchy of action from wanting to do, being able to do and being rewarded for doing. This hierarchy produces a logical flow of intervention from strengthening motivation to enabling to reinforcing the self-care behavior. A patient's need to conserve resources, however, dictates skipping those interventions not required if a patient is already motivated, enabled or reinforced. The skip pattern can be guided by a minimum of questions designed to detect the motivational state, the barriers and the potential rewards and side effects for the patient. The skip pattern can also include assessments, decision nodes and recursive loops in an algorithm for patient education, diagnosis and intervention as suggested in Figure 2.

Phase 1: The Initial Triage of Patients According to Motivation

The first question a physician or other clinical staff needs to answer is whether a patient even cares enough about the problem to bother with the prescribed regimen. This can be answered on three levels, according to the health belief model.[10]

- First, does the patient believe that he or she is susceptible to continuing problems if the recommended behavior is not adopted?
- Second, does the patient believe that the problems associated with failure to comply with the recommended behavior are severe?
- Third, does the patient perceive the benefits of adopting the recommended behavior to be greater than the perceived risks, costs, side effects, barriers and hassles?

If the answer to all three questions is yes, the patient is likely to be willing to try the recommended behavior. The physician need not lecture this patient.

If a patient is already willing, considerable time and energy otherwise spent on persuasion can be conserved for training or support. If a patient is not motivated according to these three criteria, then it would be premature to train the patient in skills or to counsel the patient to overcome barriers in the home environment. The time and resources of the physician should be spent first on educating the patient on the importance and benefits of the recommended practice. The purpose of this initial education is to strengthen the three beliefs in the patient.

In this situation written materials are no substitute for face-to-face two-way communication. In a systematic assessment of 102 controlled studies of patient education related to prescription drugs, the factors that predicted the magnitude of change in patient knowledge or beliefs, as well as in drug errors and clinical effects, were not the media or channels of communication, but rather the individual attention, relevance and feedback provided in the communication.[11]

Figure 1.—Typical relapse pattern for patients following long-term self-management regimens.

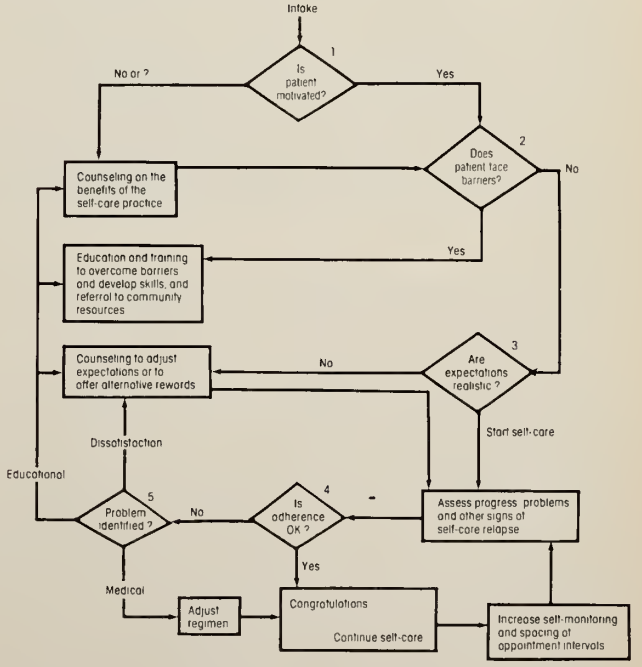

Figure 2.—A protocol is shown for stepped-care approach to counseling patients in managing their medical regimen. The flow chart was prepared for a National Heart, Lung, and Blood Institute working group and benefitted from comments by Donald Fedder, DrPH, David Levine, MD, William McClelland, MD, Patricia Mullen, DrPH, Edward Roccella, PhD, and Scott Simonds, DrPH. ◇ = decision node; □ = recommended intervention

If a patient's level of prior motivation cannot be assessed after a few direct questions, the best predictor of patient education and counseling at this first level is the years of school completed by the patient. Less formal education means a greater need for patient education.[12] This might seem too obvious to warrant mention, but an irony of medical practice is that physicians tend to talk more to patients who ask more questions—typically those of higher educational achievement—than to those who ask fewer questions but probably need more answers.[13] Regardless of the level of education, a physician can easily probe for a patient's level of understanding by asking the patient to repeat the instructions he or she is to follow.

Phase 2: Steps in Triage of Patients According to Enabling Factors

Once a physician is satisfied that a patient is motivated, the next diagnostic step is to assure that the patient is able to carry out the prescribed behavior. Problems that need to be investigated are the skills, resources and barriers in the home or work environment that the patient needs help to develop or overcome. If the patient is highly motivated and willing to try the regimen prescribed by the physician, but faces inability, lack of needed resources or barriers that cannot be overcome alone, the patient will be frustrated and ultimately discouraged. Skill deficiencies are most common in young children, arthritic patients who cannot open certain containers, illiterate or non-English-speaking patients who cannot read or understand directions, old patients whose eyesight or mobility makes adherence to certain regimens impossible and other disabled or poor patients who cannot obtain or afford the necessary resources to follow the physician's recommendations.

If any of these enabling factors are found to be deficient in a patient, the physician recommending the unattainable regimen has some obligation to help the patient find ways to overcome the deficiency. Some training of the patient in the necessary skills or modification of the regimen to fit the patient's circumstances are minimal interventions expected of the physician. At the very least, the physician owes it to the patient to provide systematic referral to other agencies or resources in the community to help deal with these enabling factors.

Phase 3: Assessing Reinforcing Factors Necessary to Patients' Adherence

Even with the predisposing and enabling factors in place, there remains one more level of possible breakdown in a patient's "compliance" with a prescribed regimen. If the recommended behavior is met with side effects, inconvenience, derision by family or friends, criticism by employer or teacher or other sources of discouragement, the patient is likely to discontinue the practice prescribed or recommended by the physician. The opposite of these discouraging factors are reinforcing factors. The physician can help build reinforcement of patient compliance in two ways.

First, the physician can provide reinforcement by assuring that the patient's expectations are realistic so that what happens during the course of the treatment is expected rather than coming as a rude shock. Side effects should be anticipated. Counseling can help prevent the relapse typically associated with the first signs of side effects.[14] Difficulties in following a diet or in stopping smoking should be described in advance, coupled with encouragement for the patient to expect and cope with them rather than to give up at the first discouraging experience or event. If a patient has unrealistic expectations about the smooth course of recovery, weight loss, abstention or adoption of a new health practice, the physician needs to correct these misperceptions before they become an excuse for giving up.

The second way in which a physician can help reinforce the adoption of a complex regimen requiring behavioral change at home or at work is to communicate directly or indirectly with family members or others in a patient's immediate circle of daily contacts. Family members can be invited to accompany the patient in discussing the prescribed regimen with the physician. Often family members are left sitting in the waiting room when they could be participating in the discussion of home strategies to support the patient in adapting the prescribed regimen to daily routines. If the important parties cannot be influenced in the physician's office, a written message to them from the physician, carried by the patient or mailed to them with the patient's permission, could carry as much weight. The power of involving family members in reinforcing support of patients has been well established.[15,16]

Phase 4: Self-monitoring

Once a physician has been assured of a patient's motivation, has addressed the enabling and reinforcing factors and has provided the counseling, referrals and support necessary to make the patient's self-care possible, return appointments can be spaced with increasing intervals. With each subsequent visit, some of what the physician examines as signs, symptoms, risk factors or problems can be made the responsibility of the patient to self-monitor. Transferring increasing responsibility for self-care to the patient should be accompanied by the patient's increasing self-monitoring skills.

Physicians miss a powerful educational tool when they hoard patients' data and the methods of observation that would make patients capable of obtaining their own feedback on progress and success in self-management. By transferring these skills and tools—such as self-monitoring blood pressure devices—to patients, physicians enable the patients to obtain more immediate feedback on adjustments they are making in their life-style or in a dietary or medication regimen.[11] Feedback from self-monitoring can over time become the most powerful source of reinforcement for positive behavior. If a patient continues to depend on the physician for this reinforcement, the patient can fail to make the conversion to self-reliance that is so essential to long-term maintenance and control coincident with chronic or compulsive disorders.

Conclusion

Sufficient knowledge has now accumulated to enable physicians to approach the problem of patient compliance with greater confidence, effectiveness and efficiency. Greater confidence should come from the accumulated evidence achieved by physicians' teaching and counseling their patients on self-medication and more complex life-style changes. Greater effectiveness should come from the increased awareness among physicians that basic principles of learning have been instrumental in transferring knowledge, skills and responsibility to patients. Greater efficiency should come from the stepped-care approach to patient education and counseling outlined in this article. By concentrating their time and effort at that level

of help needed by each patient, physicians can bypass needless motivational appeals and skill development for some patients and can target their counseling for other patients who most need these levels of help.

A physician's final maneuver in consigning greater responsibility to patients for their own care and health maintenance is to transfer self-monitoring skills and tools to them. These become both the enabling and the reinforcing factors in patients' long-term maintenance of behaviors conducive to health.

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Causes for Delay in Diagnosing Breast Cancer

THE NUMBER ONE CAUSE for delays in diagnosing breast cancer is not knowing the limits of mammography. Physicians and patients accept a normal mammogram as evidence that cancer is not present when there is a palpable mass. About 20% of cancers will not show on a mammogram with a palpable mass. Whenever I order a mammogram, I tell the patient "This is a screening test. If it's positive, it helps me; if it's negative, we have to go beyond that, and we'll discuss those choices when we get the mammogram."

The next risk is not doing a biopsy when they find something on a mammogram and cannot find a mass. Next is not doing a needle or aspiration biopsy. With a needle and syringe, I can diagnose any cyst in the breast in two minutes. And I have an absolute diagnosis; it is not just a picture. I have fluid in a syringe. If I do not have fluid in a syringe, I do either a needle biopsy or an open biopsy. If a patient has nipple discharge and it is bloody, there is a 50% chance the patient has cancer. So you must do an occult blood test on nipple discharge.

—HOLGER RASMUSSEN, MD

Extracted from *Audio-Digest Family Practice*, Vol. 35, No. 17, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Special Article

Private Financing Options for Long-term Care

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Private financing for long-term care now comes almost exclusively from out-of-pocket payments. Long-term-care costs quickly impoverish most elderly, resulting in Medicaid dependency. The consequences are profound for the western Sun Belt with its rapidly growing elderly population. Key private financing options are long-term-care individual retirement accounts (LTC/IRAs), home equity conversion, social-health maintenance organizations and long-term-care insurance. Study of data from the past half century suggests that the LTC/IRA approach would prove unsatisfactory for the purpose despite the intuitive appeal of this mechanism. Experience with home equity conversions is still very limited, and unresolved questions limit this approach to the role of a reserve option for now. While promising, social-health maintenance organizations are still in the experimental stages and not yet commercially available. Long-term-care insurance is currently sold on a thin market and emphasizes nursing home coverage. New approaches to private financing through long-term-care insurance seem to offer the best approach for immediate implementation.

(Brody BL, Simon HJ, Smallwood DE: Private financing options for long-term care. West J Med 1987 Sep; 147:350-356)

The projected growth of the nation's elderly population and implications for health care are topics of current study.[1-5] A major problem area is the financing of long-term care, much of which is now covered by Medicaid. The impact of the growing elderly population on individual states is just beginning to be assessed.[6] The focus of this article is on the nation's largest state, California. In this era of federal budget cuts in programs for the poor, however, the issues of long-term-care financing are especially relevant for all states burdened by the prospect of ever greater demands on Medicaid as the population ages.

The Growing Elderly Population in Relation to Long-term Care

In 1980 California's elderly (65-plus years) population numbered 2.5 million. By the year 2000, this segment of California's population is projected to increase by almost 45%, or more than 1 million persons. The situation in California is indicative of the rapid growth projected for the Sun Belt region. In the southwestern and western states, the elderly population is anticipated to grow by about 60% between 1980 and 2000, compared with 12.5% to 16% elsewhere in the country.[1]

The aging of the population has significant implications for financing long-term-care services, and these are likely to be exacerbated in the Sun Belt areas where the most rapid growth is expected. Among the consequences of an aging population are increases in: the number and proportion of persons with limitations of activity due to chronic conditions; physician visits; nursing home residents, and the proportion of personal health care expenditures devoted to the elderly population. In 1980, 11% of the population was aged 65 and older. These persons accounted for 29% of personal health care expenditures. By 2040, as much as 21% of the population is expected to be older than 65, and this group will consume 45% of all personal health care expenditures.[7]

At any one time, about 5% of persons aged 65 and older and 20% of those aged 85 and older are in nursing homes. The likelihood, however, that any one person will need long-term care during his or her remaining life span is much greater (see below). Furthermore, for every person in a nursing home, there are an estimated one to two equally disabled but not (yet) institutionalized elderly people.[8]

Estimated Lifetime Long-term Care Use by the Elderly

What is the probability that an elderly Californian will need long-term care in his or her remaining lifetime? Longitudinal data needed to answer this question are not available. Based on recent national estimates, between 39% and 63% of elderly Californians will spend some time in a nursing home.[9,10] Nursing home estimates are used as an indicator of long-term-care use because the few available data and projections concerning long-term care generally refer to nursing home use; nursing home services are those usually needed by the most dependent persons, and they are viewed as the most costly among the diverse long-term-care options.

The heterogeneity of long-term-care needs is indicated by simulated lifetime patterns of lengths of stay in nursing homes. The overall lifetime stay for elderly persons in a nursing home averages 555 days, but 38% are for 90 days or less. The shorter periods consist chiefly of brief convalescent or terminal-care stays. Of the remaining longer-term nursing home admissions, 23% are for 3 to 12 months, with the other

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This study was supported in part by the California Policy Seminar, Institute of Government Studies, University of California, Berkeley, and in part by the Sandoz Foundation.

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ABBREVIATIONS USED IN TEXT

IRA = individual retirement account
LTC/IRA = long-term-care individual retirement account
MCPI = medical Consumer Price Index
NHSI = Nursing Home Survey Index
RAM = reverse annuity mortgage
SCAN = Senior Care Action Network
s-HMO = social-health maintenance organization

39% being for a year or longer.[9] If these proportions are applied to the low and high ranges of per-capita risk estimates of nursing home admissions among the elderly, the proportion of elderly Californians who can anticipate nursing home or comparable long-term care experiences in the community can be estimated as shown in Table 1.

Costs for nursing home care vary widely. For purposes of this analysis, MediCal—California's Medicaid program—rates of $37 per day are used for the lower end of the range[11 (p ix)] and $97 per day for the higher end (J. Heinz, "The Search for Long-term Care Solutions," *Business and Health,* Dec 1984, vol 2, pp 5-7) to yield estimates of nursing home care costs for elderly Californians over the remainder of their lives.

Existing data do not permit precise estimates about likely lifetime long-term-care costs. For persons in nursing homes for longer than a year, and taking the ICF Inc (Washington, DC) estimated length of stay averaging 2.4 years, average charges would amount to $32,400 (low rates) or $84,000 (high rates).[9] Combining the lower limits of the (first two) length-of-stay categories in Table 1 with the low utilization estimates and the low daily charge, one gets an expected total cost for long-term care of $5,200, averaged for all persons. The upper limits and high range of estimates yield an average cost of $28,000. These data indicate that, when nursing home care is needed, costs are likely to be significant regardless of whether public or private payers have to carry the load.

Current and Projected Long-term Care Use in California

In 1980 there were 125,500 elderly Californians in nursing homes. This number is projected to nearly double to 237,900 persons by the year 2000, even though the proportion of elderly in the general population is expected to increase by only about 50%. The implications for California are profound because MediCal is the primary payer for 70% of the days spent in long-term-care facilities.[11] In fiscal year 1984-1985, the estimated MediCal expenditures for skilled nursing home and intermediate-care facilities amounted to $422,974,930.[12]

The implications are at least equally profound for individual elderly Californians and their families. Except for the rich, few elderly persons can afford to pay for the full cost of services. If receiving a pension or Social Security payments, a reasonably healthy older person or couple can live independently, but when chronic medical problems and infirmities make unassisted daily living difficult or impossible, expenses are apt to become unbearable. Only a few, limited mechanisms are available now for middle-income people to protect themselves from these costs without becoming dependent on family or public resources. Very few insurance companies offer policies covering such care, and then only with severe restrictions. The major options for such persons seem to be to become dependent on their children (if any)—and the children

TABLE 1.—*Estimated Risk of Nursing Home Admission by Length of Stay*

Length of Stay	Low Range Estimate of Risk, %*	High Range Estimate of Risk, %†
≤90 d	14.8	23.9
3-12 mo	9.0	14.5
≥1 yr	15.2	24.6
Total	39.0	63.0

*Adapted from ICF Inc.[9]
†Adapted from McConnel (estimated by applying ICF Inc distribution of lengths of stay).[10]

may themselves be elderly or of limited means, or both—or to become impoverished and dependent on the already greatly stressed public programs, principally MediCal.

Private-pay options and protection from the catastrophic costs of needed services are extremely limited. Furthermore, many who enter nursing homes as private-pay patients ultimately deplete their resources, and MediCal must then cover their expenses. With regard to noninstitutional long-term care, about 60% to 80% of the services are provided by family or friends, but not without cost.[9] The informal provision of care may impose financial losses because of foregone income by a person, often a wife or daughter, who remains at home to provide care instead of pursuing paid employment. Furthermore, the number of single or childless persons is increasing. The kinds of informal support systems available to them, if any, are not readily apparent. An examination of existing components of long-term-care services, their settings, auspices and financing conveys an impression of highly fragmented systems with lacunae in services, funding and—above all—vitally needed data.

Long-term-care financing is a complex undertaking for an increasing number of elderly persons. Indications are that any options to be developed to provide for the greater number of elderly persons needing long-term care will require still greater public or private expenditures, or both. Some of these options will be examined.

Long-term-Care Individual Retirement Accounts

Using an individual retirement account (IRA)-like mechanism to finance health care and long-term care for the elderly has recently been proposed.[13,14] This apparently prudent approach—making modest contributions into a fund over an extended period of time to build a nest egg to pay for long-term-care costs when needed—intuitively appeals to many. Accordingly, we studied the adequacy of such a mechanism as a solution to the problem of covering long-term-care costs.

To assess the feasibility and adequacy of an IRA approach to long-term-care costs, we examined how a long-term-care individual retirement account (LTC/IRA) might have performed over the past half century.[15] To determine whether investment returns would have dominated cost inflation of long-term care or vice versa, we examined the number of days that would have been covered by an LTC/IRA, assuming that each annual contribution equaled the current cost of one day of care. Using actual data on various investment options for the past half century, we determined how hypothetic IRA funds would have done in terms of the number of days of coverage that would have accumulated for contribution periods ranging from 5 to 35 years. A direct analysis of long-term-care cost trends is constrained by the scarcity of data on

these costs and use. Therefore, we used the medical care component of the Consumer Price Index (MCPI) and the Nursing Home Survey Index (NHSI) as proxies for the lack of historical data on long-term-care costs. Details of the method and results are presented elsewhere.[15]

With one exception, the analyses showed that cost inflation would have outstripped returns on the investment: the number of days the LTC/IRA fund would have covered fell far below the number of "days contributed." Furthermore, the longer the investment period, the greater the discrepancy between long-term-care days contributed and covered days available when the fund is first used. Except for the case when common stocks were used as the investment vehicle and the MCPI was used as a proxy for long-term-care cost rises, the investments would have done poorly. If the NHSI is used instead of the MCPI, then the hypothetic fund would have done poorly even if invested in common stock. While people are undoubtedly better off with a "nest egg" than without one, an LTC/IRA fund would probably not, by itself, cover long-term-care costs even for those who began making modest annual contributions to such a fund as young adults.

Home Equity Conversion and Its Potential for Financial Long-term Care

Approximately three out of four households headed by persons aged 65 and older live in owner-occupied homes. About 80% of these people own their homes outright. This group includes low-income elderly people who have accumulated equity in their homes.[16] This is of particular interest because most other private approaches to financing long-term care seem limited to middle- and upper-income groups.[14,17] Only a small proportion of elderly people, however, have more than $50,000 in home equity. This proportion tends to increase with income level and decrease with age.

In the past few years, new developments regarding home equity conversion have caused this concept to be viewed somewhat more favorably.[18-20] Specifically, home equity conversion plans have now been devised that can provide additional avenues for the elderly to maintain autonomy in the event of increased dependency resulting from chronic illness. Funds obtained through home equity conversion today are unrestricted, however, and usually are not used to finance long-term care.

Nevertheless, there are possibly serious objections to suggestions that elderly people give up ownership in their homes, even for long-term-care financing. In fact, these may be relevant for all income groups because home ownership not only provides shelter, but also is important psychologically to many people. Further, many elders wish to be able to pass some tangible assets on to their heirs. Finally, a public policy that threatens to force the elderly out of their homes is currently untenable ("State Tells Some on MediCal They Must Sell Homes," *Los Angeles Times*, Nov 28, 1984, pt I, pp 3, 20; "Rules Tying MediCal to Home Sales Suspended," *Los Angeles Times*, Nov 29, 1984, pt I, pp 3, 26) and is likely to face ever greater opposition as the population continues to age.

Major home equity conversion options and key implications for financing long-term care for the elderly are described below. The main options are reverse mortgages and special purpose loans.[20]

Reverse Mortgage Options

A reverse mortgage is a loan to a home owner based on the equity in the home. Payments are made monthly. Repayment of the principal and interest is due at the end of the term of the mortgage. The mortgage can mature in a predetermined number of years. A recent version allows repayment on the death of the owner, or on sale of the home.

The nonprofit San Francisco Development Fund developed the "fixed-term reverse mortgage" as the Reverse Annuity Mortgage (RAM) program and has been offering screening, counseling and home equity conversion options since 1981. Statewide, and as of January 31, 1986, only 188 reverse annuity mortgages and 9 "sale lease-backs" had been consummated. (Sale lease-backs are considered in more detail in the next section.)

The typical client for the RAM program is old, frail and wishes in-home long-term-care services. The interest rates and terms of the loan are fixed. Typical expenditures for in-home services from all sources range from $12,000 to $30,000 per year, with daily costs of $80 not being unusual. Because the average monthly RAM payment is $845, home equity alone will not cover all costs. The average term of a loan is 7 years, and the maximum allowable term is 12 years. Property values average $165,000 each, which is well above the national average. The maximum ceiling on loans, however, is $150,000, or 80% of the appraised market value, whichever is less. The average age of clients is in the early 80s for women and in the late 70s for men. The ability of these people to function independently is very limited.

This client profile pattern is the result of careful counseling to avoid the major limitation of fixed-term reverse annuity mortgages—namely, that a client may outlive the term of the mortgage and be forced to sell. Consequently, RAM finds that most of the loans are paid off early, within four years, when clients have died or chosen to sell their homes. There is no penalty for early repayment of the loan (Kathy Kenny, Associate Director, Reverse Annuity Mortgage [RAM] Program, San Francisco Development Corporation, written communication, March 7, 1985).

The "open-term reverse mortgage" version provides a steady stream of monthly payments until death of the home owner or sale of the house. At that time, the loan is repaid with interest and a percentage of any appreciation in the value of the home. Since August 1984, Prudential Bache has been marketing this plan, known as an individual retirement mortgage account (IRMA).

Sales Plans

The second approach to the use of home equity involves selling a house while retaining lifetime occupancy rights. One version is a sale or lease-back plan. This complex legal arrangement can be arranged directly between private parties or with assistance from corporate enterprises. Although plans differ in detail, they involve a down payment to the seller plus monthly lifetime payments and purchase of an annuity by the buyer for the benefit of the seller.

The "life-estate" version is based on a split ownership arrangement. In return for relinquishing the house at death, an elderly home owner retains conditional ownership and receives a monthly cash annuity, or a one-time lump sum payment. The buyer is responsible for home maintenance, improvements and payment of property taxes.[20] The life-estate

idea, however, was developed by a nonprofit organization to foster preservation of residential neighborhoods and not for long-term care, but a similar approach could be developed to pay for long-term-care services.

Since January 1985, a third variation of the sale or lease-back plan has been offered by the Family Backed Mortgage Association of Oakland, California (R. Guenther, "All-in-the-Family Mortgages Start to Show Some Promise," *The Wall Street Journal,* May 29, 1985, section 2, p 33 [eastern edition]). The company arranges sales or lease-backs between parents and children. Early in 1986, there were about 100 mortgages whereby parents invested in their children's home and less than 20 mortgages in which parents sold to a child. The full implications of this approach to long-term-care financing are still to be determined, particularly because the dramatic expansion projected by the firm has yet to be realized. The Family Backed Mortgage Association indicates that the use of home equity conversion to finance extensive long-term care is only appropriate for aged clients with short life expectancies, such as those in the San Francisco Development Corporation RAM program, described earlier. This is because even substantial home equity may not suffice for the needs of people with a longer life expectancy, and its use for long-term care can leave a spouse homeless. Thus, except for the very old, and preferably for single persons with a distinctly limited life expectancy, home equity conversion is best suited to provide a steady stream of income supplementation over an extended period of time and not for expensive long-term-care financing (Susan Vernon, Senior Vice President for Marketing, Family Backed Mortgage Association, oral communication, January 21, 1986).

Home Equity Conversion Linked to Long-term-Care Insurance

Studies on the potential of home equity specifically to finance long-term care for the elderly have considered the options of purchasing services—that is, about one hour of homemaker care daily—or for purchasing long-term-care insurance. It is doubtful that one hour of homemaker services would suffice for elderly patients with significant limitations in functioning. Furthermore, data are lacking on the willingness of the elderly to give up ownership of their homes to purchase currently available long-term-care insurance. Additionally, the new (1986) federal income tax law raises questions about home equity conversions. By favoring home equity loans for the under-65 population, it may reduce the equity available in later years.

Overview of the Social-Health Maintenance Organization Concept

An Innovative Delivery System to Provide Long-term Care

The social-health maintenance organization concept. Social-health maintenance organizations (s-HMOs) aim to extend the idea of the prepaid group practice to long-term-care social and health services systems. Under the auspices of the Brandeis University (Waltham, Mass) Health Policy Consortium and with funds derived from the Health Care Financing Administration and private foundations, the feasibility of s-HMOs is being tested in four project sites: the Senior Care Action Network (SCAN) in Long Beach, California[21]; Kaiser Portland Health Plan, Portland, Oregon; Ebenezer Society-Group Health, Minneapolis, and Metropolitan Jewish Geriatric Center (Elderplan), Brooklyn, New York.[22]

s-HMO insurance coverage: Payments and benefits. s-HMOs are comprehensive health and social services systems for the Medicare-eligible population. They provide Medicare-covered services, Medicare supplemental insurance coverage and specified institutional and extrainstitutional long-term-care services.

An integrated financing mechanism is used, with capitation payments covered from a combination of sources. For persons eligible only for Medicare, costs are covered through special arrangements with Medicare for covered services and monthly premiums plus private copayments. (At SCAN the annual premium is $480.) For persons eligible for Medicare and Medicaid, capitation payments are covered by Medicare and state Medicaid agencies.[23]

In contrast with most long-term-care insurance plans, benefits take the form of services instead of indemnity payments; there is no elimination period; there is a copayment schedule; there is no requirement that institutional care must be used before benefits begin (thus eliminating a bias in favor of institutionalization), and the annual maximum allowable value of services is explicitly *not* enough to cover the catastrophic costs of long-term-care services for a severely disabled person.[23]

Enrollment case mix. Adverse selection may occur as a result of attracting a high-risk population. Therefore, health status-based quotas have been established to enroll a population whose health risks represent those of the general community. SCAN is prepared to institute "queueing" to obtain an enrollment of 4,000 persons of whom 86% are healthy or slightly impaired, with 10% moderately and 4% severely impaired. Of these, 20% are eligible for Medicaid, and this group will have the same health status distribution.

Risk Sharing

Risks are shared between providers of and payers for care. Ultimately, most of the risk is being borne by the patients and by Medicaid. For SCAN, the maximum coverage is $7,500 per person per year.

Overall, the most attractive feature of the s-HMO concept is that it promises to provide comprehensive, non-institutionally biased, coordinated services at a reasonable price. The principal limitation is that service benefits are capped at $6,000 to $12,000 yearly, depending on the s-HMO site.

Despite their many attractive features, health maintenance organizations have been slow to achieve public acceptance. This has been particularly true among the elderly and was probably a factor in the s-HMO architects' decision to keep premiums competitive with "Medigap" policies—policies offered to supplement Medicare benefits—despite greatly increased long-term-care benefits. s-HMOs seem to be marketed primarily as alternatives to Medigap insurance instead of as long-term-care (nursing home) programs. Now, with an increased development of health maintenance organizations serving the Medicare population, there is growing concern that the elderly are vulnerable to being underserved, especially by entrepreneurial health maintenance organizations seeking to maximize profits. These concerns may also apply to s-HMOs.

Nonetheless, s-HMOs offer the promise of slowing down public and private long-term-care expenditures although the possibility for increases still exists. The reasonable s-HMO premiums and more services supplied in comparison with Medigap policies suggest the possibility of alternate ap-

proaches to provide for the catastrophic costs of extended long-term-care needs. We recommend continued exploration and development of s-HMOs to provide for intermediate-care needs and that combining the s-HMO concept with other approaches be considered.

Long-term-Care Insurance

Present status and potential options. Interest in developing long-term-care insurance options is rising.[17,24-29] The paucity of currently available options for private long-term-care insurance coverage is highlighted by the finding that only about 1% of nursing home costs in 1984 was paid through private insurance coverage. By contrast, 50% of nursing home costs was paid out-of-pocket by consumers, 42% by Medicaid and 2% by Medicare.[30]

Development of the market for long-term-care insurance is complicated by public (mis)perceptions of the situation. A survey by the American Association of Retired Persons showed that: members are confused about the nature and amount of long-term-care coverage they now have; they tend to overestimate the amount of coverage provided by Medicare and Medigap policies, and they tend to underestimate the likelihood that they will at some time need long-term care.[31]

Available options are still very limited and most have the following general characteristics:

- Policies are sold on a limited basis, mostly to individuals and not as a part of group coverage.
- Prior hospital admission is required before nursing home benefits can be used. If home care is included, a prior stay in a nursing home is necessary to activate coverage.
- Physician authorization is required for covered services.
- Insurance benefits are provided in the form of indemnity payments. Rates are reduced for custodial care and for home care, if these are included.
- Benefits are limited to three to four years.
- Benefits for nursing home care either do not begin until an elimination period in the nursing home is completed or it is reduced for the first part of a nursing home stay.
- Long-term-care insurance policies primarily cover nursing home care. Current options do offer protection of personal assets in the event of extended nursing home stays covered under the conditions of the policy.

One advantage of insurance as a private payment mechanism is that it provides access to nursing home care because Medicaid nursing home beds are often in short supply. Another is that the public purse would also benefit from a reduction of the load on Medicaid. From the point of view of the nursing home industry, revenues are likely to increase because more persons will be able to pay private rates, about 30% above the Medicaid rate.[9]

The limitations of currently available long-term-care insurance options follow:

- Most plans offer primarily nursing home insurance because home care benefits cannot begin until a person has spent a specified period in a skilled or intermediate care nursing facility. Granted, nursing home care is now generally viewed as the most expensive component of long-term care. It may not, however, be the most attractive or desirable option for a consumer. An estimated 10% to 40% of elderly nursing home patients could be maintained in the community if alternative services and financing were available.[8]
- It is not at all clear that a consumer who buys the plan at age 65 and maintains it through his or her predicted life span will be adequately protected from inflation or from increasing costs of care.
- In many instances, a user is required to pay for any stay of less than 90 days in a skilled nursing home. This is not as catastrophic as having to pay for the entire cost of extended stays, particularly if Medicare will cover all or part. For a person who does not have liquid assets, however, the costs ($50 per day for 90 days = $4,500) often amount to a significant part of an elderly person's annual income.

In summary, long-term-care insurance seems to be an important and viable option that could provide a significant segment of the elderly population with protection from catastrophic nursing home expenses. New approaches to long-term-care insurance should be developed to provide the following: sufficient coverage for community- and home-based care; consumer choice of the locus of care in relation to home, day care or nursing home, and adequate benefits in an environment of rising costs. A summary of all of the options discussed above appears in Table 2.

Combined Financing Approaches

An analysis of currently available private mechanisms for long-term-care financing suggests a search is needed for alternate approaches. In a comparison of social-HMO versus long-term-care insurance programs, the social-HMO service benefits and the long-term-care insurance indemnity benefits exhibit reciprocal strengths and weaknesses. Currently available long-term-care insurance coverage tends primarily to address the need for extended institutional care but provides limited or no coverage at all for impairments that could be managed in the community or at home if coverage for additional types of long-term-care services were available. One strength of the social-HMO concept is its avoidance of institutional bias through providing alternative home- and community-based care. The dollar value, however, of services covered in the social-HMO demonstration project is less than the long-term-care costs for an impaired person needing services for prolonged periods of time.

The foregoing suggests a search for possibilities of combining diverse approaches to long-term-care financing. Because social HMOs are being marketed as an alternative to Medigap coverage, and because about two thirds of the Medicare population currently buys such coverage (J. Heinz, *Business and Health,* Dec 1984, vol 2, pp 5-7), it would be reasonable to consider adding a higher premium for more extensive coverage. Two options are suggested for further study:

- Medigap plus intermediate-care benefits (social HMO), or
- Medigap plus intermediate-care benefits plus long-term-care benefits.

Service delivery could be organized through the prepaid group model (HMO), a preferred provider organization model (with built-in reviews to control inappropriate use) or a fee-for-service approach.

If a social-HMO approach were combined with currently available long-term-care insurance models, one would still encounter possibly inadequate indemnity payments and the problem of the return in benefits in comparison with long-term-care costs. For these reasons, some may prefer the flexi-

bility of a social HMO in combination with an LTC/IRA, or an LTC/IRA alone. With an IRA approach, a system for coordinating eventually needed services would have to be arranged. This could be difficult for an impaired elderly person, or it could burden an elderly spouse or other family members. Brokerage agencies have recently been formed to provide case management functions to coordinate services.[32,33]

Summary

The ultimate resolutions to the problems of long-term-care financing will undoubtedly be found among combinations involving the private sector and between the private and public sectors.

We have not addressed the precise consequences of these financial approaches in any great depth. Consideration ultimately has to be given, however, to the impacts of diverse approaches to long-term-care financing. Consideration of private financing mechanisms helps to focus attention on the possible impacts of financing decisions.

The following are viewed as key issues when considering the impacts of diverse financing mechanisms:

- Adjustments to a greater role for the private sector, including possible increases in overall long-term-care costs as more care is paid for at higher private pay rates;
- Costs to the individual, spouse and children;
- The special burdens on and support for informal care providers, especially women;
- Availability of and access to needed services;
- Monitoring the quality of in-home services;
- Individual autonomy in decision making and the relative influence of large payers, such as MediCal and private insurance carriers, with regard to decisions about long-term care, noting particularly the present institutional biases of third-party payers;
- Costs to the states and to the general public, including consideration of the possibility of cost shifting between payers, and between short- and long-term-care programs, and
- Fairness and the development of appropriate incentives, especially with a view toward rewarding or penalizing for a person's previous life-style.

The diverse approaches to long-term-care financing may have unintended effects that should be taken into account when options are considered, and should be on the agenda as decisions about long-term-care financing are formulated.

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TABLE 2.—*Private Financing Options for Long-term Care*

Option	*Advantages*	*Disadvantages*
LTC/IRA	Flexibility in use of funds	Based on historical record, serious questions arise about adequacy of coverage for long-term-care costs
	Better off with "nest egg" even if inadequate by itself	Best performing long-term investment vehicles may be too unstable for purposes of long-term-care financing
Long-term-care insurance	Protection of personal assets	Primary nursing home insurance at present, with limited to no home- or community-based care
	Increased access to nursing home beds through private payments	Questionable protection from inflation and/or increasing costs of care
	Reduction of Medicaid load	Often large deductibles
	For nursing homes, revenues likely to increase	
Home equity conversion	Permits persons relatively home equity-rich and cash-poor to remain in their homes and obtain in-house long-term-care services	Only a small proportion of the highest risk age group has enough equity in their homes to pay for costly long-term-care services
	Increases proportion of elderly persons able to buy long-term-care insurance for 5% to 10% of their income, if desired	Involves complex financial arrangements; elderly people may be exploited
		Surviving member of a couple may become impoverished and homeless if home equity is used for long-term-care costs of the other
		Savings to MediCal unclear because of unpopularity of concept among elderly
		Home equity conversion may be used for any purpose; funds may therefore not be available when long-term-care is needed
Social HMO	First-dollar coverage for a continuum of community and home-based services	Service benefits limited to $6,000 to $12,000 a year
	Professional coordination of short-term and long-term-care services through case management	As in HMOs, restricted choice of providers
	Medicare supplemental insurance coverage rates competitive with Medicare supplemental insurance coverage that does not include above two items	In practice, if social-HMO proves unsatisfactory, limited opportunities for alternate private long-term-care insurance because of age and preexistent conditions
	Reasonable copayments	
	No incentives for institutionalization	
	As in HMOs, incentives to avoid unnecessary services	
	Adequate coverage for slightly or moderately disabled persons (most of those insured)	
	Fully renewable policies at SCAN and at one of the other sites	

HMO=health maintenance organization, LTC/IRA=long-term-care individual retirement account, SCAN=Senior Care Action Network

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Jehovah's Witnesses and Blood Transfusion

REGARDING JEHOVAH'S WITNESSES and hemodilution as a blood transfusion alternative, there is a method that has been accepted by the Witness community under circumstances that are acceptable to both them and me. It requires that when we take the blood off, we do not disconnect it on its way back to the patient and that we keep it running with a continuous infusion pump at all times. We are meticulous about doing this. They have accepted that we are honest and can do this, and we have a number of these patients who come to us for this surgery. We do, however, now state emphatically that we have had to transfuse only two patients and that we are not going to allow death to occur—if it came to a life or death situation, we would get a court order. We tell the patients that beforehand. The community in the Seattle area has accepted that we do not plan to give them blood at the drop of a hat, and they have accepted this prior knowledge that, in fact, we might transfuse them if it is a matter of life or death.

—ERIC B. FURMAN, MD

Extracted from *Audio-Digest Anesthesiology*, Vol. 29, No. 2, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Pelvic Fullness, Urgency and Frequency Following Lymphadenectomy

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A 60-year-old man presents with a diagnosis of prostatic carcinoma. He previously had a negative pelvic computed tomographic (CT) scan, followed by a staging lymphadenectomy. He returns four weeks following the procedure with symptoms of fullness in his pelvis, urinary urgency and frequency. CT scans of the pelvis are shown in Figure 1.

What is the differential diagnosis?

How would you confirm the diagnosis?

How would you treat this man?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION.

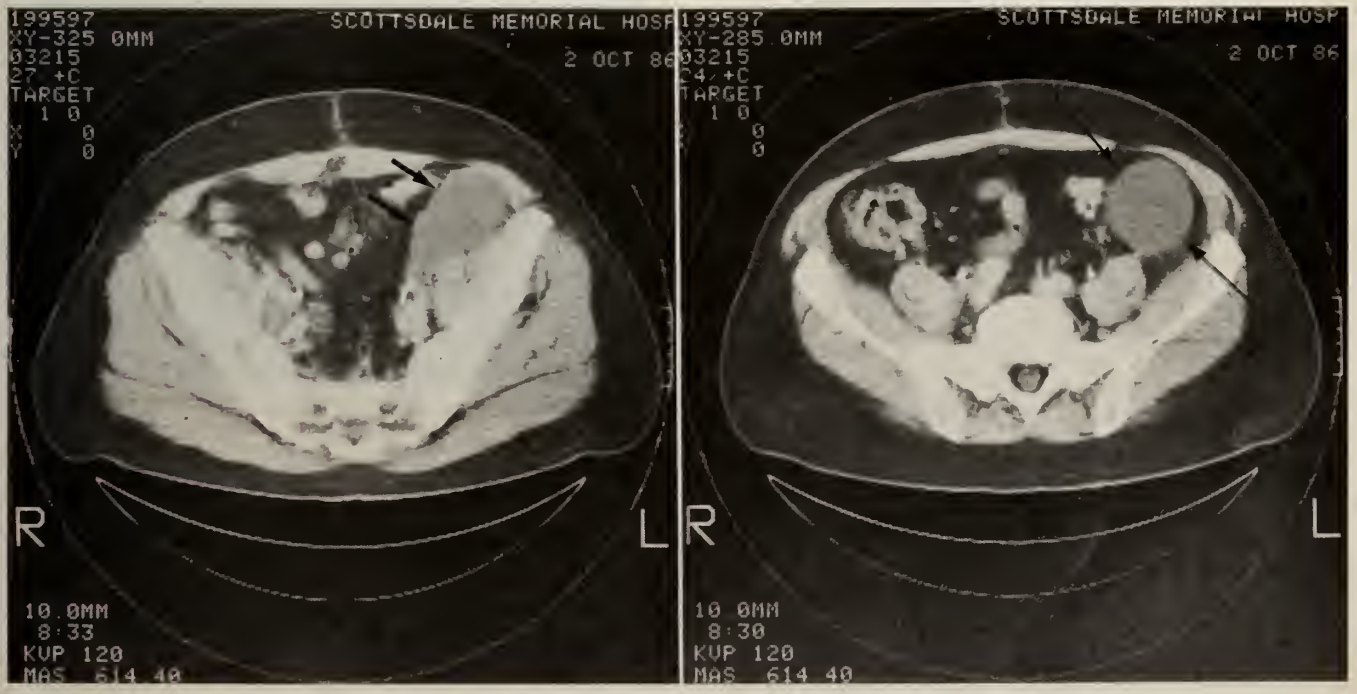

Figure 1.—Scans of the pelvis **(top** and **bottom)** show a cystic mass on the left **(arrows)**.

(Spiegel RA, Hessel SJ, Katz ER, et al: Pelvic fullness, urgency and frequency following lymphadenectomy. West J Med 1987 Sep; 147:357-358)

From the University of Arizona College of Medicine, Tucson (Ms Spiegel), and the Departments of Radiology (Drs Hessel and Levy) and Urologic Surgery (Dr Katz), Scottsdale Memorial Hospital, Scottsdale, Arizona.

Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

ANSWER: Pelvic lymphocele

The homogeneous fluid-filled mass arising from the pelvis is most likely a lymphocele. Urinoma, seroma, abscess, hematoma and homogeneous tumor mass must be included in the differential diagnosis. Although some of these can be clinically excluded in most cases, needle aspiration of the mass using ultrasound or CT guidance is a quick, simple way to define the cause of the process.

Lymphoceles result from surgical severance and inadequate closure of afferent lymphatic channels. They are a relatively common complication of major pelvic operations and occur in 25% of cases following pelvic lymphadenectomy, which is usually done for gynecologic or urologic cancer staging. They are often undiagnosed because most patients are asymptomatic. About 35% of lymphoceles are bilateral.

When lymphoceles become clinically evident, it is usually due to compressive effects due to increasing size, or to secondary infection. Many are incidentally found on follow-up abdominal imaging procedures, or at pelvic or abdominal examination. Common complaints or signs include bladder irritability, a feeling of fullness, obstructive uropathy, leg or pelvic edema or deterioration of renal function in a transplant patient. Infected lymphoceles are of particular concern in immunosuppressed patients.

Ultrasonography is the easiest method for identifying and following lymphoceles. CT is also sensitive and is most useful when ultrasonic visualization is obscured by bone or bowel gas. Using either modality, lymphoceles appear as cystic structures that arise from the pelvis and are perivascular in location (Figure 1).

Treatment of a lymphocele depends on the presenting symptoms. Because spontaneous regression is well documented, it is reasonable to follow asymptomatic lymphoceles. Needle aspiration with ultrasound or CT guidance can be therapeutic as well as diagnostic, but the recurrence rate after aspiration is high. External surgical drainage and internal marsupialization have been used in the past. Percutaneous catheter drainage is often successful and has less morbidity and mortality than surgical treatment. In this patient, CT-guided needle aspiration was done, with subsequent placement of a drainage catheter (Figure 2). Follow-up scans done two weeks after removal of the drainage tube showed no evidence of residual of the lymphocele (Figure 3).

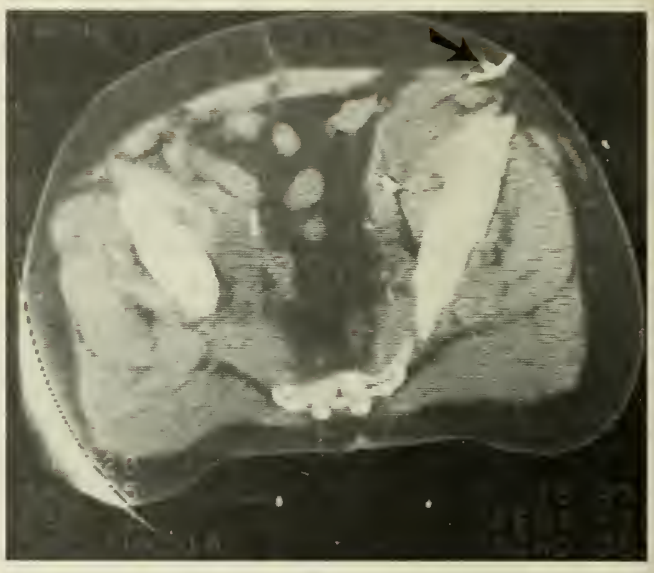

Figure 2.—A CT scan shows a catheter **(arrow)** in the lymphocele, which has decreased in size.

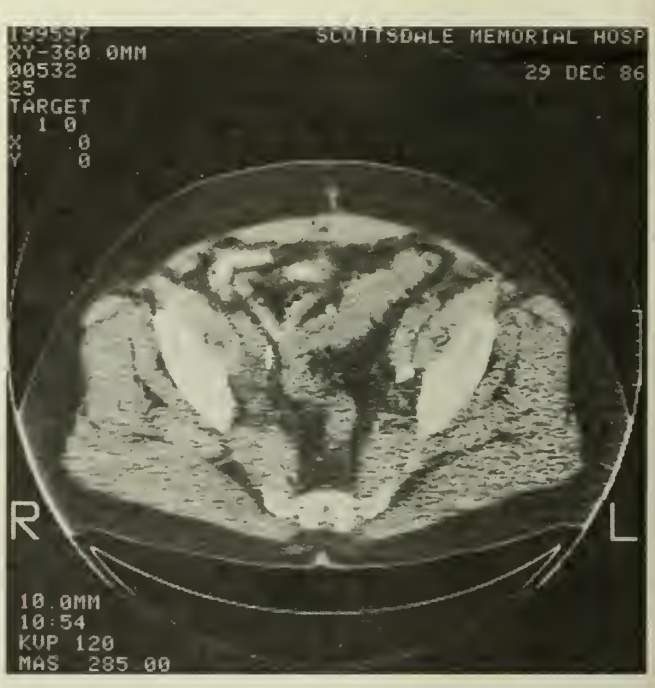

Figure 3.—A follow-up CT scan shows complete resolution of the lymphocele.

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Endoscopic Sclerotherapy for Esophageal Varices

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ENDOSCOPIC SCLEROTHERAPY, a procedure that involves injecting a sclerosing agent through an endoscope into esophageal varices, has reemerged as a popular treatment of variceal hemorrhage in the 1980s.

Most endoscopists in this country use the flexible fiberoptic endoscope and do the procedure on an outpatient basis using meperidine hydrochloride or diazepam for sedation. The use of rigid endoscopes and general anesthesia is still popular in some European countries, especially in Germany. The choice of sclerosing agent also differs between the two continents. Sodium morrhuate and sodium tetradecyl sulfate are the agents of choice in the United States, ethanolamine in England and polidocanol in other European countries. American and British endoscopists prefer injecting the sclerosing agent directly into the varix (intravariceal), while European endoscopists endorse the injection of sclerosant submucosally around the varix (paravariceal). In reality, most patients probably receive a combination of these injection methods despite the intent of the endoscopist. The treatment schedule also remains controversial. The number of treatment sessions and the interval between sessions vary among published studies, ranging from three to four treatments in two weeks after the initial session, to treatment sessions that are as long as six weeks apart. Whether the differences in techniques or timing affect the outcome remains unknown. The best evidence indicates that the efficacy of sclerotherapy in preventing rebleeding and prolonging survival will not be apparent until all variceal channels have been obliterated. This usually requires four to six treatment sessions in one to three months.

Hundreds of reports on sclerotherapy have been published in the past few years, and data from controlled randomized clinical trials are now available. To generate a consensus from the available studies, one must pay careful attention to the patients studied because the type or severity of the liver disease will influence the results of treatment. Patients with a Child's C classification and alcoholic patients who continue to drink are known to have a poor prognosis irrespective of treatment. The timing of entry into the study also influences survival data. Early mortality from variceal hemorrhage is high regardless of treatment, and those who survive the first two days after their variceal bleed have a significantly improved prognosis.[1] These factors are probably more important than differences in technique in determining the outcome in these studies. With these considerations in mind, one may dissect through the currently available data to address the following issues:

(Young HS: Endoscopic sclerotherapy for esophageal varices. West J Med 1987 Sep; 147:359-360)

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Efficacy of Emergent Sclerotherapy

Five controlled studies—three European,[2-4] one Egyptian,[5] one American[6]—have examined the effect of emergent sclerotherapy in addition to medical treatment (balloon tamponade and vasopressin). Another American study compares emergent sclerotherapy with portacaval shunt in patients with severe cirrhosis and variceal hemorrhage.[7,8] Results from these studies suggest that sclerotherapy is as effective, if not better, than medical treatment in stopping an acute variceal bleed (72% to 95%). The early rebleeding rate (20% to 50%) and one-month survival (50% to 90%), however, are not influenced by sclerotherapy.

Efficacy of Long-Term Sclerotherapy

Six randomized trials—two European,[3,4] one British,[9] one Egyptian,[5] one American[10]—compare the efficacy of long-term sclerotherapy with no therapy (splenectomy and devascularization in the Egyptian study). Results of the European and British studies suggest that sclerotherapy reduces the long-term rebleeding rate from 60% to 80% in the control group to about 40% in the treatment group. One of the European studies and the British study show that overall long-term survival is improved in the treatment groups.[4,9] While the overall survival is not improved in the other European study, mortality due to recurrent variceal hemorrhage is significantly reduced.[3] This trend is also observed in the Egyptian study where the underlying disease is primarily schistosomiasis. The only US study available also supports the observation that long-term sclerotherapy reduces the rebleeding rate, but overall survival rates are not improved. A South African study also shows no reduction in mortality after long-term sclerotherapy.[11] The control group in this study, however, received periodic sclerotherapy when variceal bleeding recurred. These studies, taken together, indicate that long-term sclerotherapy is able to reduce the risk of recurrent variceal hemorrhage and may improve long-term survival when compared with no therapy. Recurrence of varices after obliteration is observed in a rate of 60% to 70% in these studies, suggesting the need for follow-up treatment sessions to maintain this benefit.

Preliminary results from a study comparing long-term sclerotherapy with distal splenorenal shunt suggest that combining sclerotherapy with a shunt operation may further reduce the mortality rate.[12] Two recent studies compare sclerotherapy with long-term administration of propranolol hydrochloride, and the results are in conflict.[13,14] No conclusions can be drawn on this topic as the efficacy of propranolol therapy remains controversial.

Efficacy of Prophylactic Sclerotherapy

Because the early mortality is high in variceal hemorrhage, there is enormous interest in preventing the index bleed with the hope of improving long-term survival. Two randomized trials from Germany suggest that prophylactic sclerotherapy significantly reduces the bleeding (6% to 9% in treatment groups versus 57% to 66% in control groups) and mortality rates (6% to 23% in treatment groups versus 42% to 55% in control groups) in a 6- to 25-month follow-up period.[15,16] Another German study also reports a reduction in bleeding rate, but reduced mortality is seen only in Child's A

patients.[17] Preliminary data, however, from a large Veterans Administration cooperative trial on alcoholic men with cirrhosis suggests that mortality is actually two times higher in patients treated with prophylactic sclerotherapy.[18]

Prophylactic sclerotherapy, therefore, cannot be recommended as a routine treatment and should be offered only in clinical trial settings.

Complications

Complication rates of sclerotherapy vary widely among studies. Significant complications will develop in 10% to 15% of patients treated with sclerotherapy.[19] Hemorrhage from esophageal ulcers is probably the most common life-threatening complication, followed by esophageal perforation (1% to 5%) and esophageal strictures (1% to 7%). Tachycardia, low-grade fever and transient substernal discomfort are common after each treatment session. Pleural effusions may develop in as many as 50% of patients, but probably less than 2% require a thoracentesis. Other rare complications reported are the adult respiratory distress syndrome and spinal cord paralysis.

In summary, the efficacy of endoscopic sclerotherapy for variceal hemorrhage is still uncertain. Current data suggest that sclerotherapy can stop acute variceal bleeding but does not prevent early rebleeding nor increase early survival rates. Long-term sclerotherapy for patients who survive the index variceal bleed probably reduces the rebleeding rate and may improve long-term survival. Prophylactic sclerotherapy cannot be endorsed for routine clinical application at the present time.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 284)

January 31-February 5—**Biennial Western Conference on Anesthesiology: 1988 Clinical Update in Anesthesiology.** Toussaint Hospital Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. 22.5 hrs. $375. Contact: Murray G. Atnikov, c/o Box F110-63, Baline, WA 98230. (604) 874-5291.

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Westin Maui, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiology, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

September 19—**Third Annual Cancer Conference.** St. Agnes Medical Center at Total Life Center, St. Agnes Medical Center. Sat. 5 hrs. $35. Contact: Carol Witham, St. Agnes Medical Center, 1303 E Herndon Ave, Fresno 93710. (209) 449-3570.

October 19-21—**11th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 21 hrs. $350. Contact: Nomi Feldman, Scripps Memorial Hospital, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 29-30—**Update on Common Cancer for the Primary Care Physician: Breast, Colon and Prostate.** UCSF. Thurs-Fri. 12 hrs. Contact: UCSF.

November 6—**Managing Breast Cancer.** Sutter Community Hospitals at Red Lion Inn, Sacramento. Fri. 7 hrs. $75. Contact: Sutter Community Hospital, CME Dept. 2020 I St, Ste D, Sacramento 95814. (916) 446-7681.

December 3-5—**Recent Advances in Occupational Cancer.** Northern California Occupational Health Center and UCSF at Miyako Hotel, San Francisco. Thurs.-Sat. $220. Contact: UCSF.

December 9—**23rd Northern California Cancer Conference.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th and The Esplanade, Chico 95926. (916) 891-7300.

December 12—**Bronchology Laser Cancer Symposium.** UCI at Long Beach. Sat. Contact: UCI.

February 4-6—**Third International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. 19 hrs. $310. Contact: UCSD.

February 25-27—**Second International Conference on Intracavitary Chemotherapy.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 18 hrs. $300. Contact: UCSD.

CARDIOLOGY

September 17-18—**Optimal Coronary Revascularization.** Santa Barbara Medical Foundation Clinic, Sansum Medical Clinic and Santa Barbara Cottage Hospital at Red Lion Resort Hotel, Santa Barbara. Thurs-Fri. 14 hrs. $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sun. 13 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

September 25-27—**International Workshop on Future Directions in Interventional Cardiology.** American College of Cardiology at Red Lion Resort, Santa Barbara. Fri-Sun. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (800) 253-4636, ext 226, or (301) 897-5400.

September 30—**Drug Therapy for Ventricular Arrhythmias.** Cedars Sinai Medical Center at Cedars Sinai Medical Center, Los Angeles. Wed. Contact: Lore Kahane, Cedars-Sinai Medical Center. PO Box 48750, Los Angeles 90048. (213) 855-5547.

October 15-17—**11th Annual Seminar: Cardiology Update 1987.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

October 15-17—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 30-31—**Coronary Heart Disease.** Medical Education Resources at Las Vegas Hilton Hotel, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 13-14—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hilton Hotel, San Francisco. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 14—**16th Annual Cardiology Symposium.** Fresno Community Hospital at Center Plaza Hotel, Fresno. Sat. Contact: Joann Ellis, Fresno Community Hospital, PO Box 1232, Fresno 93715. (209) 442-3936.

December 3-4—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Beach Marriott, Newport Beach. Thurs-Fri. Contact: UCI.

December 4-5—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

January 22-24—**Advanced Cardiac Life Support,** CPR Seminars at Ralph K. Davies Medical Center. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 28-30—**Clinical Nuclear Cardiology.** ACC at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 11-13—**Second Annual International Symposium: Clinical Strategies in Complex Valvular Heart Disease.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 16 hrs. $350. Contact: UCSD.

DERMATOLOGY

October 24-25—**16th Annual Mycology Review.** STAN at STAN. Sat-Sun. Contact: STAN.

EMERGENCY MEDICINE

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550.

October 29-November 1—**Traumatic Brain Injury 1987: A Meeting of the Minds-Science and the Injured Brain.** UCD at Red Lion Motor Inn, Sacramento. Thurs-Sun. 30 hrs. $395. Contact: UCD.

INTERNAL MEDICINE

October 10—**Clinical Update on Thromboembolic Disease and Anticoagulation.** UCD at Hilton Hotel, Sacramento. Sat. Contact: UCD.

October 10—**Update in Diagnosis and Therapy for Infectious Diseases.** Cedars Sinai at Harvey Morse Conference Center, Cedars Sinai Medical Center. Sat. 5 hrs. $100. Contact: Cedars Sinai Medical Center, Room 2049, PO Box 48750, Los Angeles 90048. (213) 855-5547.

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 28—**Endocrinology Ninth Annual Symposium**-Hospital of the Good Samaritan at Moseley-Salvatori Conference Center. Wed. 5.5 hrs. $90. Contact: Mary Anne Clark, 616 South Witmer St, Los Angeles 90017. (213) 977-2335.

November 11—**Gastroenterology.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

January 19-23—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton, Beverly Hills. Tues-Sat. 40 hrs. Contact: UCLA.

(Continued on Page 363)

CONTINUING MEDICAL EDUCATION

(Continued from Page 362)

February 7-12—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Incline Village. Sun-Fri. 18.5 hrs. $365. Contact: UCSF.

March 4-5—**Gastrointestinal Endoscopy 1988.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Fri-Sat. Contact: David S. Cantor, MD, 50 Alessandro, Ste 410, Pasadena 91105. (818) 793-7114.

March 11-17—**Internal Medicine 1988: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Thurs. 54 hrs. $495. Contact: Jackie Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

September 19-22—**The Fetus and Newborn.** Contemporary Forums at San Diego. Sat-Tues. Contact: Contemporary Forums, 530 La Gonda Way, Ste E, Danville 94526. (415) 820-2800.

October 16-18—**Advanced Fetal Heart Rate Monitoring.** UCI at Embassy Suites Hotel, Napa Valley. Fri-Sun. Contact: UCI.

November 15-21—**10th Annual Review Course in Clinical Obstetrics & Gynecology and/or Gynecological Histopathology** at UCI. Sun-Sat. Contact: UCI.

November 16-20—**18th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

December 4-5—**Environmental Exposure and Fetal Development (March of Dimes).** UCD at Sacramento Inn. Fri-Sat. Contact: UCD.

January 18-22—**19th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

February 7-11—**16th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki. Sun-Thurs. Contact: Ohio State University, 410 W 10th Ave, Columbus, Ohio 43210. (614) 293-8487.

OPHTHALMOLOGY

October 17—**Glaucoma 1987: Medical and Surgical Management of Secondary Glaucoma.** National Society to Prevent Blindness and Estelle Doheny Eye Institute at Le Meridien Hotel, Newport Beach. Sat. 7 hrs. $175. Contact: Daniel J. Sigband, MD, National Society to Prevent Blindness, 249 E Emerson Ave, Ste F, Orange 92665. (714) 974-EYES.

December 10-11—**Ophthalmic Plastic and Reconstructive Surgery: Past, Present, and Future—A Tribute to Crowell Beard, MD.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

PATHOLOGY

October 3—**Fine Needle Aspiration Tutorial.** UCSF at UCSF. Sat. 7 hrs. $475. Contact: UCSF.

PEDIATRICS

October 10-17—**11th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea Beach, Hawaii. One week. Contact: UCI.

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 16-18—**Current Advances in Pediatrics.** American Academy of Pediatrics and UCI at Disneyland Hotel, Anaheim. Fri-Sun. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

October 23-25—**Current Concepts in Pediatric Gastroenterology.** Children's Hospital, Oakland at Doubletree Hotel, Monerey. Fri-Sun. Contact: Kim Leadon, CME Office, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

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Samuel Hellman, MD
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Section of Plastic & Reconstructive Surgery
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CONTINUING MEDICAL EDUCATION

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October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

November 20-23—**9th Annual Las Vegas Seminars—Pediatric Update.** Los Angeles Pediatric Society at Caesar's Palace. Fri-Mon. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 4-6—**Current Concepts in Pediatric Medicine—1988.** Childrens Hospital and Health Center, San Diego at Holiday Inn, Embarcadero, San Diego. Thurs-Sat. Contact: Children's Hospital San Diego. 8001 Frost St, San Diego 92123. (619) 576-1700.

February 20-27—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Royal Lahaina Resort, Maui. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

PSYCHIATRY

October 9-11—**First Annual UCLA National Conference on Preventive Psychiatry**—The Prevention of Mental Health Disturbances in Childhood. UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Sun. 12 hrs. $175. Contact: UCLA.

October 10-11—**Focusing on the Female Patient: Advances in the Management of Common Disorders.** Cypress Foundation and Western Regional of AMWA at Hyatt Regency Hotel, Monterey. Sat-Sun. 10 hrs. $145. Contact: Bob Meyer, Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

October 17-18—**Dynamics of Human Development—Implications for Treatment.** Continuing Education Seminars at Los Angeles. Sat-Sun. 11.5 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave, Los Angeles 90024. (213) 475-8300.

November 6-8—**33rd Annual: Group Therapy Symposium.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sun. Contact: UCSF.

November 7-8—**The Resistant Patient: Differing Perspectives of Classical Psychoanalysis and Self-Psychology.** San Diego Psychoanalytic Society and Psychonanalytic Institute at San Diego. Sat-Sun. Contact: San Diego Psychoanalytic Institute, 1010 Turquoise St, Ste 320, San Diego 92109. (619) 488-0687.

November 30-December 1—**Behavioral Science as an Approach to Accident Prevention.** USC. Mon-Tues. 1.4 hrs. $375. Contact: USC.

January 21-24—**Health Science Response to Child Maltreatment—1988.** Children's Hospital and Health Center ar Hanalei Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Children's Hospital and Health Center, 8001 Frost St, San Diego 92123. (619) 576-1700.

RADIOLOGY

September 17-19—**Ultrasound Workshop.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

September 26-27—**Magnetic Resonance Imaging With Interpretive Workshops.** Los Angeles Radiological Society at Registry Hotel, Universal City. Sat-Sun. 10 hrs. $200. Contact: Los Angeles Radiological Society, PO Box 91215, Los Angeles 90009. (213) 642-0921.

October 17-18—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. Contact: UCSF.

October 19-23—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. $495. Contact: UCSF.

October 19-23—**12th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 28 hrs. $425. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 24-31—**Radiology for Emergency & Primary Care Physicians.** American Institute of Postgraduate Education and Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Kona, Hawaii. One Week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 3586, La Jolla 92038. (619) 454-3212.

SURGERY

September 26-27—**Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at Los Angeles. Sat-Sun. 12 hrs. Contact: Terri Harrington, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 4-10—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 5—**Wrist Arthroscopy.** American Society for Surgery of the Hand at San Diego. Mon. Contact: Paula Scheid, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 17-18—**Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at San Francisco. Sat-Sun. 12 hrs. Contact: Terri Harrington, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-24—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 21—**Primary Care Course.** American Society for Surgery of the Hand at Los Angeles. Sat. 7 hrs. Contact: Anne Turner, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 6-12—**Temporal Bone Surgical Dissection—1987.** House Ear Institute at House Ear Institute, Los Angeles. Sun-Sat. 62 hours. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

September 16—**Common Office Pediatric and Dermatology Cases.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

September 19—**AIDS: A Multidisciplinary Approach to Care in 1987 and Coming Years.** Sutter Community Hospitals at Sacramento Inn, Sacramento. Sat. 6.5 hrs. $55. Contact: Sutter Community Hospital, 2020 I Street, Ste D, Sacramento 95814. (916) 446-7681.

September 20—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Sun. 7 hrs. $195. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-22—**7th Annual Bristol-Myers Symposium on Nutrition Research: Nutrition and the Origins of Disease.** UCD at Fairmont Hotel, San Francisco. Mon-Tues. 15 hrs. $100. Contact: UCD.

September 30—**Drug Therapy for Ventricular Arrhythmias.** Regional Arrhythmia Center at Cedars-Sinai Medical Center, Los Angeles. Wed. 5 hrs. Contact: Lore Kahane, Cedars-Sinai Medical Center, 8700 Alden Dr, Los Angeles 90048. (213) 855-5547.

October 7-10—**PSEF International Tissue Expansion Symposium.** Plastic Surgery Educational Foundation at Westin St. Francis Hotel, San Francisco. Wed-Sat. 26 hrs. $600. Contact: PSEF, 233 N Michigan Ave, Ste 1900, Chicago, IL 60601. (312) 856-1818.

October 9-10—**Caring for Alzheimer's Disease Victims: Practical Aspects.** UCSD at Horton Grand Hotel, San Diego. Fri-Sat. 12 hrs. $175. Contact: UCSD.

October 9-10—**Twelfth Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute, Dominican Hospital at Chaminate Conference Center, Santa Cruz. Fri-Sat. $300. Contact: Karen Rickenbach, Dominican Neurologic Institute, Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7706.

October 10—**Lasers in Medicine: Expanding Clinical Applications.** Alta Bates Hospital, Berkeley. Sat. 7.5 hrs. $65. Contact: Mary Grim, Alta Bates Hospital, 3001 Colby St, Berkeley 94705. (415) 540-0337.

October 14—**17th Annual Respiratory Medicine.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 364)

October 16-18—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $365. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-22—**Annual Family Practice Update.** Mon-Thurs. LLU at LLU. Contact: LLU.

October 19-30—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI at Long Beach. Mon-Fri. Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

October 22-24—**West Coast Counties Postgraduate Institute.** California Medical Association at Sheraton Hotel, Monterey. Thurs-Sat. 12 hrs. Contact: Janice Rigney, CMA, PO Box 7690, San Francisco 94120-7690. (415) 863-5522, ext. 416.

October 24-31—**Ninth International Seminar on Operative Arthroscopy.** UCLA at Marriott Resort Hotel, Maui. One week. 30-36 hrs. $850. Contact: UCLA.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 26-November 1—**Traumatic Brain Injury.** UCD at Red Lion Motor Inn, Sacramento. Mon-Sun. Contact: UCD.

November 2-6—**Sampling and Evaluating Airborne Asbestos Dust.** USC. Mon-Fri. 3.5 hrs. $725. Contact: USC.

November 10-13—**Industrial Ventilation Fundamentals.** USC at USC Study Center, San Diego. Tues-Fri. 2.8 hrs. $675. Contact: USC.

November 12-14—**2nd Annual: Progress in Impotence—Workshops/Seminars.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. 13 hrs. $295. Contact: Edith Bookstein/UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 18—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service, (117) VAMC, 16111 Plummer St, Sepulveda 91343. (818) 891-2473.

November 22—**Controversy in Modern Medicine—1987.** Granada Hills Community Hospital and UCLA at Sheraton Universal Hotel, N Hollywood. Sun. 7 hrs. $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021.

December 7-18—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

February 2-4—**11th Annual: Neurology for Non-Neurologists.** UCSD and Neurology for Non-Neurologists Foundation at Holiday Inn Embarcadero, San Diego. Tues-Thurs. 21 hrs. $395. Contact: Edith S. Bookstein/NNN, PO Box 3586, La Jolla 92038. (619) 454-3212.

February 11-13—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

February 13-15—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs. Sat-Mon. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262. (619) 325-5588.

February 19-21—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs at Desert Hospital. Fri-Sun. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

MONTANA

October 1-3—**Montana Medical Association—Annual Meeting.** Copper King Inn, Butte. Thurs-Sat. Contact: MMA, 2012 11th Ave, Ste 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 19—**Practical Management of Diabetic Foot Infections.** Veterans Administration Medical Center, Albuquerque. Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

September 24-26—**Concepts and Controversies in Perinatal Care.** Holiday Inn Journal Center, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME. (505) 277-3942.

September 24-26—**Wilson Lectureship—Cardiology Symposium.** Albuquerque. Thurs-Sat. Contact: Presbyterian Heart Institute Cardiology Symposium, PO Box 26666, Albuquerque 87125. (505) 841-1065.

October 1-3—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

October 7-December 1—**History of Medicine Seminar—Prehistory to the Eighteenth Century.** David A. Bennahum, MD, Instructor. Medical Center Library, University of New Mexico, Albuquerque. 4-6 pm, Tuesdays.

October 9—**Health Care in America: Stewardship of a Finite Resource—Lovelace Foundation 40th Anniversary Program.** Holiday Inn, Journal Center. Fri. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque 87108. (505) 262-7194.

October 9-10—**Balloon Fiesta Lung Disease Symposium.** VA Medical Center, Albuquerque. Fri-Sat. Contact: NM Lung Assn, (505) 265-0732.

October 10-11—**Pediatric Chronic Diseases.** Santa Fe. Sat-Sun. Contact: Marilyn Stack, Executive Secretary, New Mexico Pediatric Society, (505) 265-7431.

October 23—**Update in Cardiology.** Albuquerque. Fri. Contact: Charles Karaian, MD, 1101 Medical Arts Ave NE, Albuquerque 87102. (505) 842-8321.

October 23-25—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Fri-Sun. Contact: The Presbyterian Heart Institute, Barry W. Ramo, MD, (505) 242-2796.

November 13-14—**New Mexico Medical Society Interim Meeting—Risk Management.** Sally Port Inn, Roswell. Fri-Sat. Contact: NMMS, (505) 266-7868.

December 3-5—**American College of Physicians, New Mexico Chapter—Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

December 11-12—**Trauma Update '87.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

January 5-March 1—**History of Medicine Seminar—Modern Medicine.** David A. Bennahum, MD, Instructor. Medical Center Library, University of New Mexico, Albuquerque. 4-6 pm, Tuesdays.

February 26-28—**16th Annual Thoracic Society Lung Disease Symposium.** Santa Fe Hilton. Fri-Sun. Contact: Lung Association, (505) 265-0732.

March 25-27—**Santa Fe Ski Symposium—Hypertension—1988.** Santa Fe. Fri-Sun. Contact: National Kidney Foundation of New Mexico, 1715 Girard, NE, Albuquerque 87106. (505) 266-4573.

(Continued on Page 370)

24-hour security for the hypertensive heart

First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial O_2 demand

Preserves K^+ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

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First-step protection for the hypertensive heart

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Tablets
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**)
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0 24 sec); systolic blood pressure < 100 mmHg, or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously Both digitalis and Lopressor slow AV conduction
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic The response should be observed closely If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken Patients should be warned against interruption or discontinuation of therapy without the physician's advice Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures
Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e g , tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure
During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued
Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients, this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered
AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0 26 sec), second-, or third-degree heart block Acute myocardial infarction also produces heart block
If heart block occurs, Lopressor should be discontinued and atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered
Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may oe required Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician
Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined, (2) to contact the physician if any difficulty in breathing occurs, (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase
Drug Interactions
Catecholamine-depleting drugs (e g , reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia Neither finding represents symptoms of a known disease entity in man In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor
All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative
No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55 5 times the maximum daily human dose of 450 mg Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal These studies have revealed no evidence of impaired fertility or teratogenicity There are no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug Caution should be exercised when Lopressor is administered to a nursing woman
Pediatric Use
Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients Depression has been reported in about 5 of 100 patients Mental confusion and short-term memory loss have been reported Headache, nightmares, and insomnia have also been reported
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients Cold extremities, arterial insufficiency, usually of the Raynaud type, palpitations, congestive heart failure, peripheral edema, and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**)
Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**)
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients
Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients Worsening of psoriasis has also been reported
Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients Musculoskeletal pain, blurred vision, and tinnitus have also been reported
There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable
The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear
Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27 4%	23 2%
Bradycardia (heart rate < 40 beats/min)	15 9%	6 7%
Second- or third-degree heart block	4 7%	4 7%
First-degree heart block (P-R ≥ 0 26 sec)	5 3%	1 9%
Heart failure	27 5%	29 6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients
Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear
Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor
Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**)
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death
Oral LD_{50}'s (mg/kg) mice, 1158-2460, rats, 3090-4670
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure
Treatment
There is no specific antidote
In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**)
On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed
Elimination of the Drug: Gastric lavage should be performed
Bradycardia: Atropine should be administered If there is no response to vagal blockade, isoproterenol should be administered cautiously
Hypotension: A vasopressor should be administered, e g , levarterenol or dopamine
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered
Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

Geigy GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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CALIFORNIA FORENSIC MEDICAL GROUP, INC, a corporation providing medical services in California county jails, has opportunities for physicians with a specialty in either Family Practice, General Practice or Internal Medicine. Send résumé to CFMG, Inc, PO Box 1831, Salinas, CA 93902; or contact Elaine Hustedt (408) 422-0214.

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PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full- or part-time for FP/IM/EM trained/experienced physician. Located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900-100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or (206) 582-2542.

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ARIZONA EMERGENCY MEDICINE. An emergency department Medical Directorship and staff positions are immediately available at two client hospitals located in Kingman and Lake Havasu City. Moderate volume emergency departments. Excellent nursing and medical staff support. We offer a guaranteed competitive rate of compensation, occurrence malpractice insurance coverage, CME allowance, reimbursement of professional dues. Directors also receive paid health benefits which include dependents. For additional information contact George Tracy, Spectrum Emergency Care, 6275 Lehman Dr, Ste C-202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

FAMILY PRACTICE/INTERNAL MEDICINE/ENDOCRINOLOGY/CARDIOLOGY/OCCUPATIONAL MEDICINE physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing southwest community (population 500,000 plus). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics/Internal Medicine/Subspecialties/24-hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with CV to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

SAN FRANCISCO—ONE HOUR. Multispecialty group in a growing community is now accepting applications for positions available in Family Practice and Internal Medicine. First year includes guaranteed salary plus incentive. Excellent benefits including malpractice, life, health and disability insurance. Send CV to Number 51, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

IDAHO NEEDS FULL-TIME EMERGENCY PHYSICIAN. 20 miles from Boise, near mountains and unlimited recreation. Excellent opportunity to affiliate with 162-bed hospital. ACLS-yes. Contact M. Kutsurelis, Vice President Administrative Services, Mercy Medical Center, 1512 12th Ave Road, Nampa, ID 83651; (208) 467-1171.

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GENERAL SURGEON BC/BE. Excellent opportunity to associate in a busy surgical practice in Sonoma, California, one hour drive north of San Francisco. Contact J. Basil Haddad, MD, 181 Andrieux St, Sonoma, CA 95476; (707) 996-6119.

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FAMILY PRACTICE PHYSICIAN. Full-time, in walk-in medical clinic, Visalia, Tulare County, California. Salary, malpractice insurance, etc. For additional information, contact Brenda Baker, Director of Business Services, (209) 627-5555.

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(Continued on Page 376)

CONTINUING MEDICAL EDUCATION

(Continued from Page 366)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

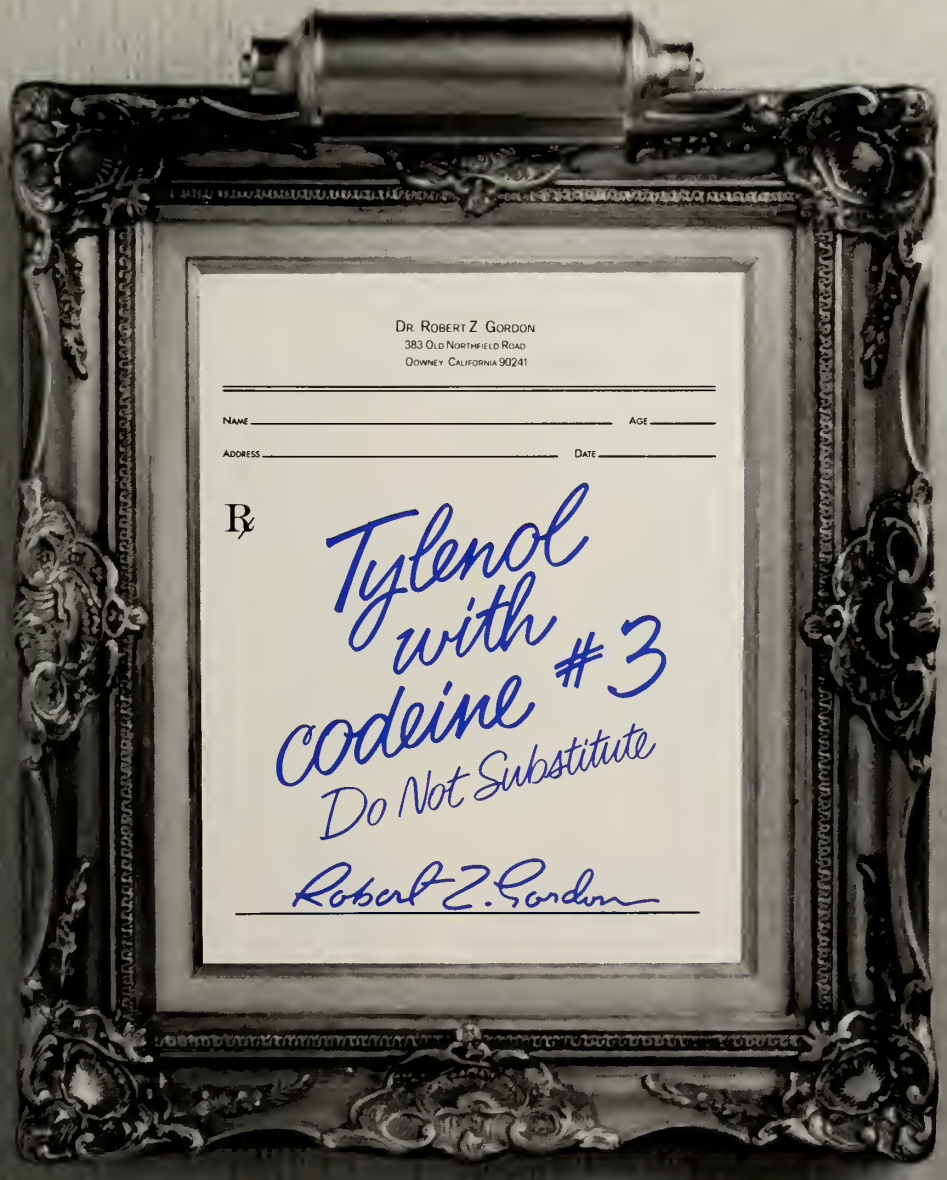
UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 374)



CREATE A SIGNED ORIGINAL

to be sure your patients get...

Tylenol®

ACETAMINOPHEN

with codeine phosphate

TABLETS Ⓒ III ELIXIR Ⓒ V

Tablets: Contain Codeine Phosphate*: No. 3—30 mg; No. 4—60 mg—plus Acetaminophen 300 mg.

Elixir: Each 5 mL contains 12 mg Codeine Phosphate* plus 120 mg Acetaminophen (Alcohol 7%).

*Warning: May be habit forming.

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TYCT 6445-A

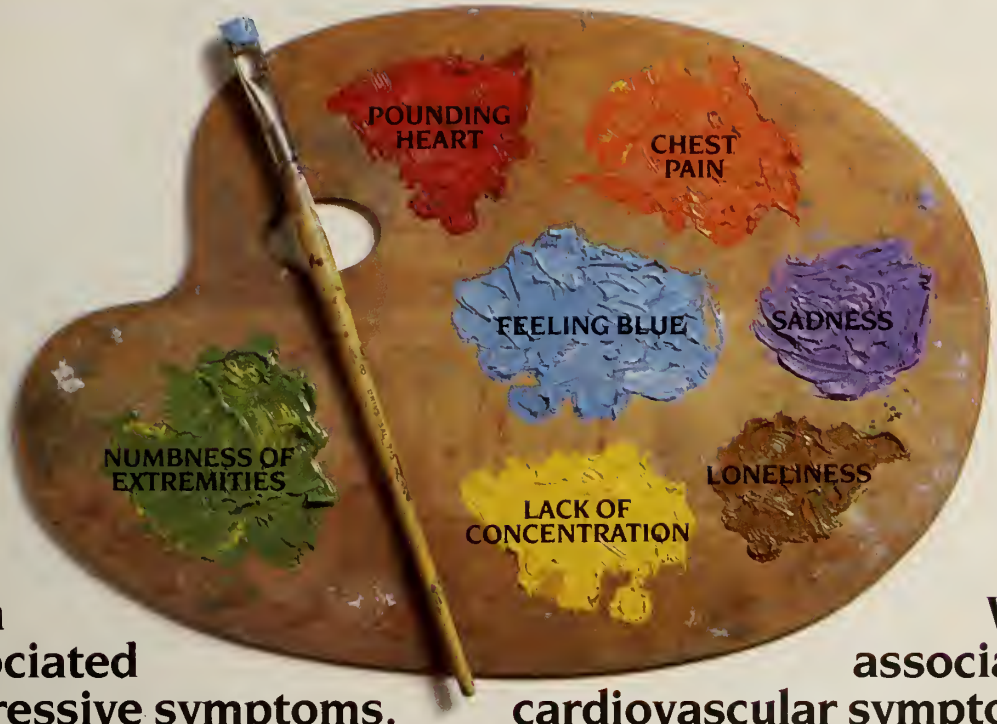
The portrait of anxiety

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

©1987 The Upjohn Company

is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA
J-7384
February 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 370)

February 8-13—**Utah Ophthalmological Society Annual Winter Meeting** (Sponsor: UOS). Mon-Sat. Little America Hotel, Salt Lake City. 15 hrs. Contact: Carol Leavitt, (801) 355-7477.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

September 21-22—**Total Hip Replacement.** The Inn at Semiahmoo, Blaine. Mon-Tues. Contact: U/W.

October 1-2—**American College of Emergency Physicians—17th Annual Fall Scientific Assembly.** Seattle. Thurs-Fri. Bellevue Red Lion Inn. Contact: Washington Chap, ACEP, (206) 441-9762.

October 11-16—**National Society for Histotechnology—1987 Symposium/Convention.** Seattle. Sun-Fri. Contact: VMMC.

October 14—**Psychological Aspects of Occupational Health.** Seattle. Wed. Contact: UW, (206) 543-1069.

October 15-17—**Annual Review of Neurosurgery.** Seattle. Thurs-Sat. Contact: U/W.

October 16—**Psychosis: What's New, What's True.** Seattle. Fri. Contact: U/W.

October 16—**21st Annual Cancer Conference: Breast Cancer—Issues Faced by the Primary Care Physician & Patient.** Seattle. Fri. Contact: VMMC.

October 29-31—**Orthopedic Review.** Seattle. Thus-Sat. Contact: VMMC.

November 5-6—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

November 6-7—**Cardiology Update.** Seattle. Fri-Sat. Contact: VMMC.

November 12-13—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 13-14—**New Concepts in Laser Therapy: A Symposium.** Seattle. Fri-Sat. Contact: VMMC.

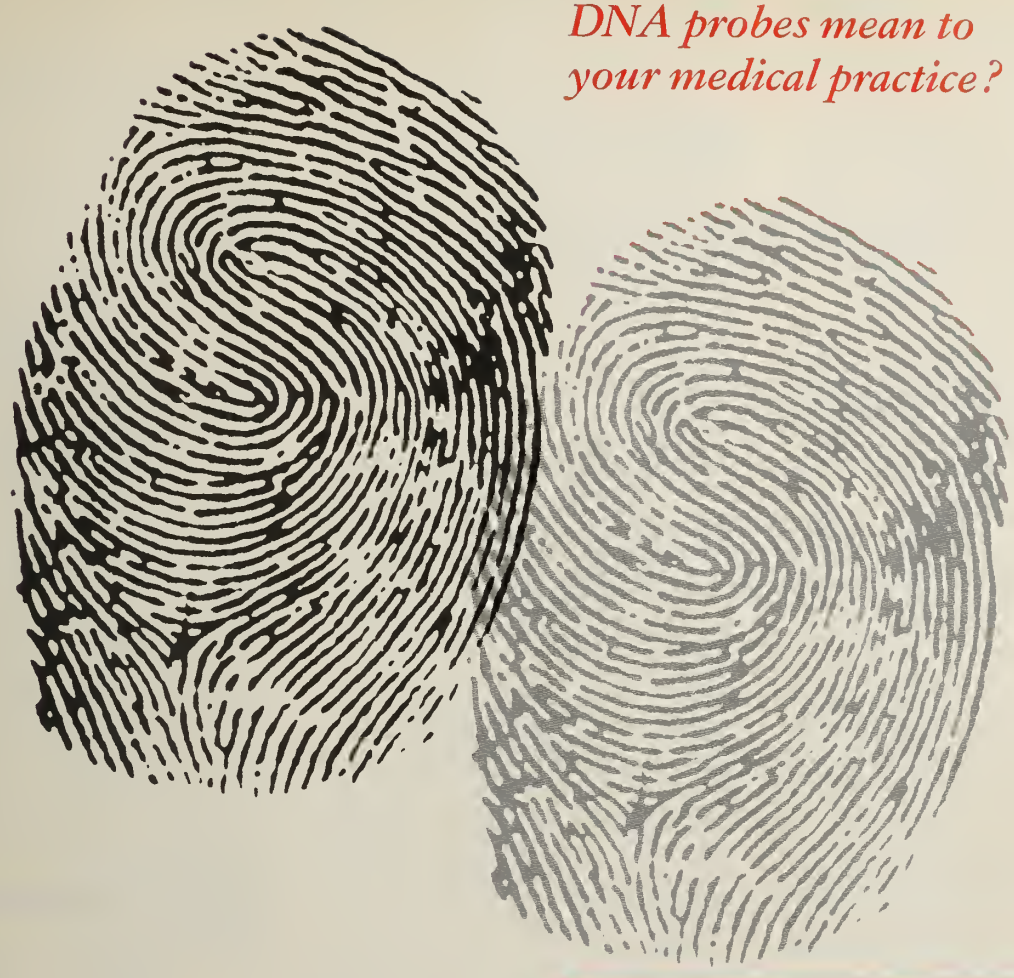
November 20-21—**Innovations in Newborn Care: A Challenge for the 90s.** Seattle. Fri-Sat. Contact: NW Hospital, (206) 364-2229.

November 27-December 10—**Emergency and Critical Care Down-under.** Sites in New Zealand and Australia. Fri-Thurs. Contact: Washington Chapter, American College of Emergency Physicians, Georgine Elich, Kailani World Travel, 1 (800) 542-5264 or (206) 671-1800.

December 5—**Medico-Legal Aspects of Neurology.** Seattle. Sat. Contact: U/W.

December 11—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC. ◆

What will the use of DNA probes mean to your medical practice?



Biotechnology and Medicine Series

Second AMA Conference on DNA Probes in the Practice of Medicine

November 13-14, 1987
Bonaventure Hotel
Los Angeles, California

DNA probes are quickly developing into a powerful new tool for the diagnosis of disease. Join us for the *DNA Probes in the Practice of Medicine* conference, and gain an understanding of how DNA-based diagnostics are being applied to your specialty.

Through a combination of lectures and workshops, the conference will cover the basic concepts underlying the use of DNA probes; demonstration of hybridization techniques; clinical settings in which DNA probes will become routine; objective assessment of the accuracy, sensitivity, and reproducibility of DNA Probes in clinical diagnosis; and the ethical and legal issues confronting physicians in the screening of genetic diseases.

Materials on this conference will be available soon. To receive yours, please contact:

R. Mark Evans, Ph.D.,
Office of Biotechnology
American Medical Association
535 N. Dearborn Street
Chicago, Illinois 60610
(312) 645-4567.

(Continued from Page 369)

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

ORTHOPEDIC SURGEON. Opportunities throughout the midwest and Colorado. These positions offer both general orthopedic practices, along with subspecialized training. Partnership and group settings. Contact Jean Malkasian, 250 Regency Ct, Waukesha, WI 53186; (414) 785-6500, collect.

DIRECTOR OF THE RESIDENCY TRAINING PROGRAM. Full-time faculty position available in the Department of Family Practice, University of California, Davis. Level of appointment commensurate with academic experience and credentials. Must be Board certified by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research and academic publication activities. The position will remain open until filled. Applications will not be accepted after December 31, 1987. Send CV to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

NONINVASIVE CARDIOLOGIST—BC/BE to join busy Invasive Cardiologist in San Jose, California. Early partnership. Expertise required in all noninvasive activities including: Nuclear Cardiology, 2D-Doppler and echo. Also, Swan-Ganz and pacemaker insertion. Please send CV to Number 50, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA—BEAUTIFUL CENTRAL COAST AREA. Nine man, multispecialty group with focus on primary care, seeks a BC/BE Family Practice physician, with preference given to those who include obstetrics. Location in a major rural growth area demands that we recruit to service increased patient volumes. Be prepared to step into an active practice with group conveniences and rewards. Ocean and mountains are an added plus. Excellent salary/fringe benefit package leading to partnership buy-in opportunity. Telephone inquiries welcomed and/or address CV to Valley Medical Group, Patrick M. Quigley, Sr, Administrator, 136 N. Third St, Lompoc, CA 93436; (805) 736-1253.

FAMILY PRACTICE PHYSICIAN, BC/BE. Scenic northwest. Immediate opening. System of four primary care community clinics. Full-scope family practice, new facilities, excellent salary and fringes, terrific staff. EOE. Send résumés to Dr Richard Witt, Medical Director, Community Health Care Delivery System, 1702 Tacoma Ave S., Tacoma, WA 98402-1709.

WASHINGTON, OREGON. Practice opportunities in urgent care and emergency department settings throughout the northwest. Malpractice provided in most locations. Competitive salaries. Recreational activities abound. Write or call L. Poschman, Northwest Emergency Physicians, 11808 Northup Way, Ste 110, Bellevue, WA 98005; (206) 828-6799.

INTERNIST BC/BE—to be second Internist in a satellite of a 36-physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural and educational opportunities. Send CV to Search Committee, 55 W. Tietan, Walla Walla, WA 99362.

PHYSICIANS WANTED

CALIFORNIA, SAN FRANCISCO BAY AREA. Major HMO seeking BC/BE Emergency Physician to join staff of active Emergency Department in large, urban, academically-oriented medical center. Competitive salary, outstanding fringe benefits, and shareholdership are among the many advantages of joining Kaiser Permanente, the nation's leading HMO. Please address all inquiries to William Barnaby, MD, Emergency Department, Kaiser Permanente Medical Center, 280 W. MacArthur Blvd, Oakland, CA 94611.

THE WALLA WALLA CLINIC, a 36-physician multispecialty clinic, is seeking a second physician to staff an established and growing walk-in Immediate Care Center. Excellent benefit package in a beautiful pacific northwest community with excellent recreational, cultural and educational opportunities. Send CV to James Mercer, MD, 55 W. Tietan, Walla Walla, WA 99362.

WASHINGTON/PUGET SOUND. BC/BE General Internist and Family Practice (OB) positions open in large multispecialty group one block from major hospital. Located in Puget Sound, a short distance to the mountains, and access to three major universities afford our physicians a high-quality life-style and academia. Excellent practice opportunity with good starting salary and full range of benefits. Please reply with CV to Dr William Brand, President, PO Box 5467, Tacoma, WA 98405; (206) 627-9151.

VICE PRESIDENT MEDICAL SERVICES. Offers challenging opportunity to systems oriented physician for Prepaid Health Plan and fee-for-service medical center(s). Excellent salary and fringe benefits. Requires California medical license; one year of formal training in health administration or two years experience in medical care management and proficiency in primary clinical care. Please submit CV to James M. Clayton, CEO, FHFA, PO Box 30051, San Jose, CA 95156-9985. EOE.

CARDIOLOGIST, INVASIVE. 160-physician, multispecialty, prepaid group located in the San Francisco bay area wishes to add another Cardiologist/Internist. Practice includes large volume of referrals for invasive procedures. Doppler-echo skills required. University affiliation available. Please contact Larry Lawrence, MD, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119.

LOS ANGELES, CALIFORNIA. Exciting opportunity for a BC/BE Physiatrist. Excellent starting salary and benefits. For consideration, please send CV to Bryce Martin, care of The Orthopaedic Rehabilitation Institute, 181 N. Hudson Ave, Pasadena, CA 91101. Mr Martin may be contacted at (818) 795-9524.

ONCE IN A LIFETIME OPPORTUNITY. Large general practice and clinic for sale by General Practitioner preparing for retirement. Practice is part of a progressive and rapidly expanding community located in central Minnesota near excellent winter and summer recreation. Current clinic grosses over $500,000 annually, is expandable and equipped with surgery, x-ray, lab and set up for pharmacy. Fee for service and growing! Malpractice insurance not a serious problem. Computerized; excellent staff. Great potential for aggressive GPs, FPs, Internists or Surgeons. Excellent hospital one mile. Contact Janet K. (612) 251-9191.

SOUTHERN CALIFORNIA—PALOS VERDES/TORRANCE. FP/IM physician with acute care skills needed to join primary care/ambulatory care practice. State-of-the-art hospital affiliated facility located in highly desirable coastal community. Fee-for-service with administrative opportunities and early partnership status. Contact J. Lewis, MD, Executive Director, 505 Maple Ave, Torrance, CA 90505; (213) 618-9200.

FULL-TIME POSITION Available now for Family Practice physician in Vancouver, Washington. Call Helen Mosier, (206) 256-4500.

PHYSICIANS WANTED

NEPHROLOGIST/INTERNIST. Opening available in 160 plus physician group. Join additional Nephrologist/Internist in a busy and fulfilling HMO practice in the San Francisco bay area. Excellent working conditions. Ample opportunities for house staff teaching, clinical faculty appointment, cooperative group participation. Competitive salary. Superb benefit package. Reply with CV to Joseph Mason, MD, Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119. An Equal Opportunity/Affirmative Action Employer.

GASTROENTEROLOGY position available with 35-member multispecialty group for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

FAMILY PHYSICIAN. Thriving private practice along the Rio Grande in south central New Mexico seeks Family Physician. Discover New Mexico's most frequented vacation spot for outdoor and water sports. Practice offers $6,000/month plus incentives to start. Malpractice paid. OB a must. Contact New Mexico Health Resources, PO Box 27650, Albuquerque, NM 87125. No fee placement service.

INTERNAL MEDICINE—SAN FRANCISCO BAY AREA. Immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical house staff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, and retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119.

MEDICAL

PRIMARY CARE PHYSICIANS

Health Maintenance Organizations... they're what the future of health care is all about. And Maxicare is the largest investor-owned HMO. Our 2.3 million members are served by 60 health plans in 28 states.

Opportunities are currently available for Board Certified or Board Eligible Family Practioners, Pediatricians, Internists and Psychiatrists to serve our members in the San Francisco East Bay Area.

Maxicare/HealthAmerica offers a competitive salary and benefits package including employer vacation, CME time and a 401k plan. For immediate and confidential consideration, please send your C.V. to: Maxicare/HealthAmerica Northern California, Attn: Henry Loubet, Executive Director, Dept. WJM, 1 Bay Plaza, Suite 210, Burlingame, CA 94010. Equal Opportunity Employer.

maxicare

(Continued on Page 378)

When considering professional liability protection, choose the Mutual Protection Trust

Specialty	1987 CAP/MPT Estimated Cost*
Allergy	$ 2,371
Anesthesia	15,840
Cardiology with invasive vascular procedures	10,924
Cardiology — no invasive vascular procedures	5,222
Dermatology — no radiation or hair transplants	5,222
Gastroenterology with endoscopy and ERCP, board certified	8,073
Family Practice — no surgery	5,222
Family Practice — minor surgery or assisting at surgery	8,073
Family Practice — major surgery	17,905
General Surgery	17,905
Internal Medicine with invasive vascular procedures	10,924
Internal Medicine — no invasive vascular procedures	5,222
Neurology — no electro-convulsive therapy	2,371
Ophthalmology with surgery or laser	8,073
Orthopedics with spinal surgery	22,035
Orthopedics — no spinal surgery	19,970
Otolaryngology — doing plastic surgery, board certified	17,905
Pediatrics — General	2,371
Pediatrics — General, with invasive vascular procedures	10,924
Plastic Surgery, board certified	17,905
Psychiatry — no electro-convulsive therapy	2,371
Radiology — diagnostic, no coronary angiography	5,222
Radiology — including coronary angiography	10,924
Urology	13,775

*These rates include dues and assessments for a CAP/MPT member with 50 or more months of membership or retroactive coverage (matured rate). CAP/MPT offers coverage limits of $1 million per occurrence with an aggregate of $3 million per year.

CAP/MPT offers:

- **EXPERIENCE: The oldest California Trust providing professional liability protection**
- QUALITY: Stringent screening process — each member has a voice in the selection of new members
- **SAVINGS: Compare our cost with other experienced providers of malpractice protection**
- REINSURANCE: Limits assessment exposure
- **LOSS PREVENTION PROGRAMS: Education reduces malpractice risk**
- RETROACTIVE COVERAGE: For qualified members

In addition to dues and assessments, CAP/MPT members pay a one-time initial trust contribution based on risk classification. This can be paid in installments and is refundable under the terms of the MPT Agreement.

MUTUAL PROTECTION TRUST

Cooperative of American Physicians, Inc.

P.O. Box 76998
Los Angeles, CA 90076-0998

(800) 252-7706

Call to find out what your cost would be with MPT

(Continued from Page 376)

PHYSICIANS WANTED

INTERNAL MEDICINE, INTERNIST

BC/BE general Internist needed for full-time position at Kaiser Permanente, a large HMO with excellent benefits. Located in east San Francisco bay area. Reply with CV to Winslow Wong, MD, Dept. of Internal Medicine, The Permanente Medical Group, Inc, 39400 Paseo Padre Parkway, Fremont, CA 94538.

CALIFORNIA, OREGON AND WASHINGTON. BE/BC General Surgery practice opportunities available. Excellent compensation, practice package, income potential in communities offering high quality of life. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220-4199; (503) 256-2070.

NORTHERN CALIFORNIA FAMILY PRACTITIONER wanted to join group of three Family Practitioners and one Surgeon. No initial overhead, income guarantee. Modern office across from 55-bed community hospital with staffed ER. Contact Paul E. Bartschi, MD, 225 Spruce St, Gridley, CA 95948; (916) 846-5655.

FAMILY PRACTICE position available with 35-member multispecialty group; for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

MEDICAL DIRECTOR—ARIZONA. Major telecommunications company with position opening for Medical Director in Phoenix. Prefer physician with training in Occupational Medicine and experience in medical program management. Salary and benefits competitive. Reply with résumé and names of three current professional references to Number 57, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHWEST WASHINGTON community of 60,000 seeks additional Psychiatrist for private practice and admissions to 27-bed voluntary unit in 228-bed hospital. Serve on patient care team and share hospital coverage with four other Psychiatrists. Income guarantee and group practice potential. Contact The Friedrich Group, Inc, 9284 Ferncliff Northeast, Bainbridge Island, WA 98110; (206) 547-7850 or (206) 842-5248.

INTERNIST. Live in San Francisco and commute to nearby rural area for four two-night shifts per month in combined Internal Medicine-Emergency Room practice. Four Internists currently working in stable group. Practice quality medicine in the country where you can make a greater impact and enjoy lots of free time wherever you like to live. 72K per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

OTOLARYNGOLOGY position available with 35-member multispecialty group; for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

MONTANA. General Internal Medicine opportunity available immediately to associate with established, excellent Internal Medicine practice. ABIM necessary. Outdoorsman's paradise. Send CV to Ron Loge, MD, 401 Barrett, Dillon, MT 59725, or PROSEARCH, a division of Brim and Associates, 305 NE 102nd Ave, Portland, OR 97220-4199.

EUGENE, OREGON. Well-established, eight-physician Family Practice group is seeking BC/BE Family Physician with interest in OB. Anticipate partnership after one year. Exceptional cultural and recreational opportunities. Home of University of Oregon. Please send CV to Rob Daugherty, MD, or Kendall Hills, MD, River Road Medical Group, 2400 River Rd, Eugene, OR 97404, or call (503) 688-7527.

PHYSICIANS WANTED

ACUTE CARE WARD PHYSICIANS. $2,199-$2,424 biweekly. Four BC Internists and BC/BE Family Physicians with geriatric interest needed for acute ward (24 full-time MD staff) of large long-term care facility. 40 hour week with various schedules—some nights. Academic programs being developed. Excellent benefits. Deadline for application is October 15, 1987. Please send CV to Mary Anne Johnson, MD, Medical Director, Laguna Honda Hospital, 375 Laguna Honda Blvd, San Francisco, CA 94116. EOE. M/F/H.

OREGON COAST. General Internist and Family Practice including Obstetrics needed for busy Seaside multispecialty group. Well-equipped seven-year-old office next to 34-bed certified hospital with ICU/CCU unit. All BC group consists of three Family Practitioners, one Internist and two General Surgeons. Retirement/vacation area offers top-notch school system and excellent array of activities. Located just 75 easy miles from Portland adds even more cultural and shopping opportunities. Contact and/or send CV to Rick Bigger, North Coast Medical Center, PC, 727 Wahanna Rd, Seaside, OR 97138; (503) 738-9551.

DERMATOLOGIST AND DERMATOLOGICAL SURGEON. Large group practice with five offices in Los Angeles and Orange County has immediate openings for a BC/BE Dermatologist and a Dermatological Surgeon. A California license is required. This is an unusual opportunity for the right candidate with excellent interpersonnel skills and ability to start full-time as soon as possible. We are offering an exceptionally high salary (Dermatologist @ $125,000 plus bonus; Dermatological Surgeon @ $250,000 plus bonus). Excellent benefit package includes malpractice and health insurance coverage. For information call 1 (213) 276-3140 or send your CV to General Manager, 435 N. Roxbury Dr, Ste 210, Beverly Hills, CA 90210.

GASTROENTEROLOGIST WANTED. Solo GI practitioner with busy, established, downtown, teaching hospital practice looking for associate to start July 1988 or sooner. Must be BC/BE, endoscopically adept, and enjoy pacific northwest life-style. Send CV to Number 55, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MEDICAL RESEARCH ASSOCIATE. Biomedical R&D firm seeks laboratory associate with knowledge and expertise in organization and execution of large scale biological sample acquisition, laboratory reagent formulation, liquid chromatography and immunoassay development. MD degree, background in clinical medical science and clinical trials experience required. $30,000 per year. Job site and interviews: Mountain View, California. Send this ad and résumé to Job No. SK 6984, PO Box 9560, Sacramento, CA 95823-0560, no later than October 8, 1987.

PATHOLOGIST-AP-CP. To join three Pathologists, each of whom has subspecialty, in all new 18,000 square foot department. 300-bed hospital in northwest US. Work load requires fourth. Will be responsible for Micro and Infection Control, in addition to regular rotation. Preferably has advanced degree or fellowship in Microbiology. Competitive income, enviable climate with year 'round outdoor activities. Send CV with reply to Number 56, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTITIONER. Tulare County is seeking a BE/BC Family Practitioner to practice in an outpatient clinic which includes inpatient duties, with 14 physicians. Ability to perform simple OB required. The county provides a benefit package which includes malpractice insurance coverage. Consider a semirural life-style with cultural amenities of metropolitan areas easily accessed and Kings Canyon and Sequoia National Park nearby. Salary $89,724—$94,296 annually. Send CV to Tulare County Personnel, 2900 W. Burrel, Visalia, CA 93291; (209) 733-6266; Equal Opportunity Employer.

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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties.

Western States Physician Services
407 S. Clovis Ave, Ste 108, Fresno, CA 93727
(209) 252-3000.

EXCELLENT TEXAS OPPORTUNITIES. ENT, Family Practitioner, General Practitioner, General Surgeon, Internal Medicine, OB/GYN, Ophthalmologist, Oncologist, Pediatrician, to practice in one of several lake area communities, in the beautiful Piney Woods area of east Texas. Enjoy boating, fishing, hunting year 'round. Excellent quality of life, first year guarantee, etc. Other Texas opportunities available also. Reply with CV to Medical Support Services, Armando L. Frezza, 11509 Quarter Horse Trail, Austin, TX 78750; (512) 331-4164.

ARIZONA. Emergency Medicine practice opportunities in the Phoenix metropolitan area. Active practice with double physician coverage; expanding group. Desirable location offering many outdoor recreational and cultural opportunities. Send CV to Ms Nancy Hayward, 1400 S. Dobson Rd, Mesa, AZ 85202 or call (602) 833-6180.

RADIOLOGIST—NORTHWEST. Seven-physician Radiology group needs a full-time associate with interventional/angio training and/or experience to practice in community 300-bed hospital. Occasional outpatient clinic rotations. Send CV to B. E. Faber, MD, 2500 Cherry Ave, Ste 202, Bremerton, WA 98310; (206) 779-7765.

INTERNAL MEDICINE. Full-time position or a BC/BE Internist for a group practice in the southern San Francisco bay area. Nutrition background preferred. Opportunities for Stanford Clinical faculty appointment with Family Practice residency program. Contact Bob Thorn, 675 E. Santa Clara St, San Jose, CA 95112; (408) 977-4460.

ONCOLOGIST, SAN FRANCISCO BAY AREA. Five-man group practice needs to replace retiring Oncologist. Practice includes Oncology and Internal Medicine. Position available July 1988. Send CV to Number 54, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PHYSICIAN. Residency trained. BE/BC. Immediate opening in a busy office. OB optional. Current partners are also clinical faculty at UC Davis. Excellent community and hospital. Woodland is 15 miles from Sacramento and Davis; one hour to San Francisco bay area and two hours to Lake Tahoe. Contact James Barrett, MD, WJ Blevins Medical Group, 3 Court St, Woodland, CA 95695; (916) 662-4671.

INFECTIOUS DISEASE PHYSICIAN. BC/BE wanted to join established Infectious Disease practice in highly desirable southern California location. Excellent opportunity to do full-time Infectious Disease with or without Internal Medicine. Early partnership, arrangements flexible. First year guarantee. Send CV to Number 53, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

HOLBROOK, ARIZONA. A community of 7,000 only one and one-half hours from Flagstaff has an excellent opportunity for a BE Family Practitioner doing Obstetrics. Practice assistance includes first-year salary guarantee, free rent, and malpractice insurance. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070.

INTERNAL MEDICINE position available with 35-member multispecialty group; for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

(Continued on Page 379)

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The position is one of a kind. A frontier in which you must be creative enough to meld together the contradiction of assisting your patients to gain mental freedom while providing close custody supervision in a prison setting.

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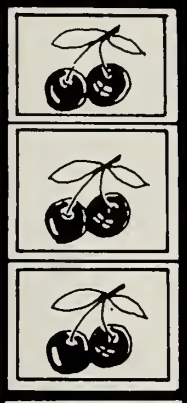

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(Continued from Page 378)

PHYSICIANS WANTED

OB/GYN. Tulare County is looking for a BC/BE OB/GYN to practice in a outpatient clinic, which includes inpatient duties, with 14 physicians. The county provides a benefit package that includes malpractice insurance coverage. Consider a semi-rural life-style with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $98,112-$103,116 annually. Send CV to Tulare County Personnel, 2900 W. Burrel, Visalia, CA 93291; (209) 733-6266. Equal Opportunity Employer.

NEUROLOGIST/ANCHORAGE, ALASKA. Outstanding solo private practice opportunity available with option to share offices with one of three busy solo Neurologists, who will provide cross coverage. Offices are located adjacent to our 238-bed hospital. Anchorage, population 200,000 plus, is the hub of the state of Alaska and a sportsman's paradise. For further information call toll-free (800) 626-1590, or send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438.

SPOKANE, WASHINGTON. Busy Pediatric practice needs third physician. Attractive offices adjacent to 230-bed hospital with 1,000 deliveries per year and a 12-bed Pediatric unit. Family-oriented community of 171,000 provides a blend of western life, outdoor recreation and urban attractions. Income guarantee and partnership. Contact The Friedrich Group, Inc, 9284 Ferncliff Northeast, Bainbridge Island, WA 98110; (206) 547-7850 or (206) 842-5248.

FAMILY PRACTITIONER. For southern California multispecialty group. Guaranteed salary plus incentives. Malpractice and health insurance provided. Spanish speaking a plus. Send CV to Atlantic Avenue Medical Clinic, 7503 Atlantic Ave, Cudahy, CA 90201; (213) 562-3500.

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CALIFORNIA. Emergency Medicine/Ambulatory Care. Join our partnership of established Emergency and Ambulatory Care physicians. PT, FT, and directorship positions available from beautiful northern California to San Diego. Excellent compensation, incentive package, and growth opportunity. Malpractice insurance provided, benefits package available. Prefer BC/BE. If you're interested in a secure and rewarding career position, contact California Emergency Physicians, 440 Grand Ave, Ste 500, Oakland, CA 94610; (415) 832-6400.

PEDIATRICIAN/COLORADO. A Pediatrician is needed in the fast-growing northern Denver suburb of Thornton. Offices located next to our 172-bed Humana Hospital—Mountain View. Attractive financial package. Send your CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free (800) 626-1590.

NEUROLOGIST/PACIFIC NORTHWEST. Purchase, for a minimal cost, practice of a Neurologist in Tacoma, Washington, who is retiring soon because of health. He sees approximately 800 new patients a year, and EEG, EMG and evoked potentials can be done in office. CT and MRI testing available. For further information, send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free (800) 626-1590.

THE UNIVERSITY OF WASHINGTON seeks individual at Assistant Professor level. Must be BC in Nephrology, trained in both clinical and experimental studies of metabolic bone disease, experienced in performing and interpreting bone biopsies and have independent grant or career development award. Contact W. Couser, MD, Head, Division of Nephrology, RM-11, University of Washington, Seattle, WA 98195. The University of Washington is an Equal Opportunity Employer.

PHYSICIANS WANTED

UROLOGIST/PHOENIX, ARIZONA. A busy, 39-year-old Urologist is seeking an associate to join his thriving private practice. The offices are located near our new hospital in suburban Paradise Valley. For more specific information, call toll-free (800) 626-1590, or send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438.

THE COMMUNITY OF ARTESIA, NEW MEXICO is seeking a BC/BE General Surgeon to establish a private practice. Fully-equipped office with established referral patterns available for purchase. Community-based financial assistance may be available to the right individual. Artesia is a community of 14,000 located in southeast New Mexico. A great place to raise a family—peaceful community with year 'round recreation and excellent weather. Fully-equipped, 38-bed new hospital. Please submit CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1-800-545-4030, ext 8300.

WASHINGTON. Openings for career oriented Emergency Physicians, BC/BE in Emergency or primary medical specialty. In a Seattle metropolitan hospital with 35,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 South 43rd St, Renton, WA 98055.

GERIATRICS/PACIFIC NORTHWEST. The director of the Geriatrics Unit at our 155-bed hospital in Tacoma, Washington, is seeking an associate who possesses a fellowship or training in Geriatrics. For more information about this opportunity, send your CV to Gordon Crawford, Humana Inc, Dept. GG-8, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free (800) 626-1590.

EMERGENCY MEDICINE. San Francisco bay area. BE/BC Emergency Physician for part-time, potential full-time, starting November 1, 1987 at Kaiser Hospital in San Rafael, and then joining new Santa Rosa Kaiser Hospital in 1988/1989. Competitive salary, outstanding benefits, AA/EOE employer. Contact John David, MD, Chief, Emergency Department, Kaiser San Rafael, 99 Montecillo Rd, San Rafael, CA 94903.

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INTERNIST, ENDOCRINOLOGIST, BE. Trained at UCSF. Prior outpatient Primary Care experience. Desires position consisting of General Internal Medicine and specialty in San Francisco bay area. Reply to Number 49, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MAJOR UNIVERSITY CENTER TRAINED INTERNIST-GASTROENTEROLOGIST. Currently junior faculty in GI, competent in all GI procedures including therapeutic ERCP as well as general Internal Medicine. Looking to join GI or IM multispecialty group in coastal California in July 1988. California license. Speak medical Spanish, French, Russian. Please write PO Box 1035, Brookline, MA 02146.

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64-YEAR-OLD GENERAL RADIOLOGIST. Experienced; two years diagnostic ultrasound. Seeks locums. BC, licensed—California, Arizona, and state of Washington. Write 218 Villa Dr, King City, CA 93930; or call (408) 385-5893 or (408) 385-6672.

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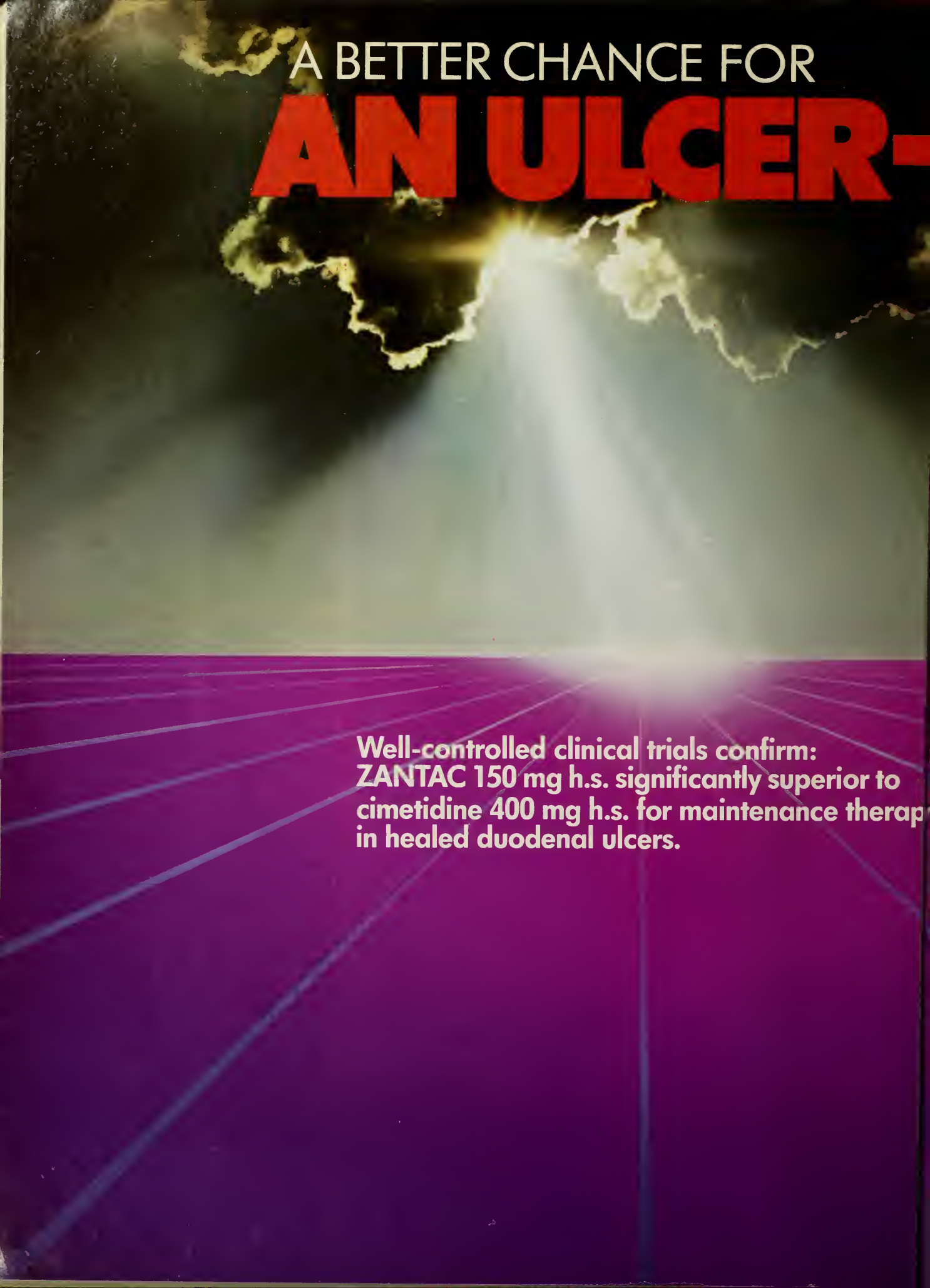
(Continued on Page 382)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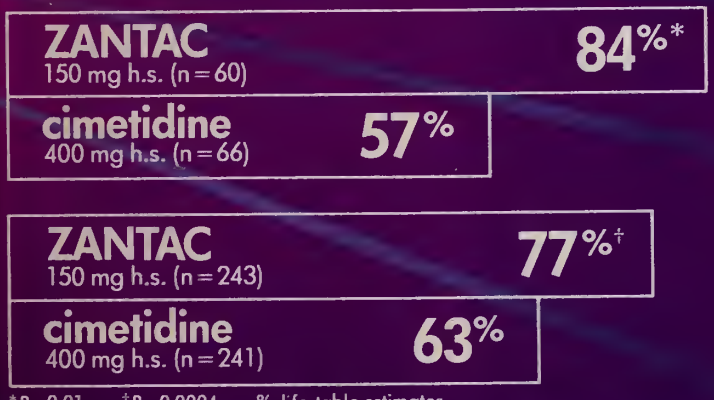
in healed duodenal ulcers.

FREE FUTURE

Percent of patients ulcer-free after 1 year of therapy



*P = 0.01 †P = 0.0004 % life-table estimates

All patients were permitted prn antacids for relief af pain.
Adapted fram Silvis[1] and Gough[2]

These twa trials[1,2] used the currently recommended dasing regimen of cimetidine (400 mg h.s.) and ranitidine (150 mg h.s.). A comporison af ather dosing regimens has not been studied.
The studied dosing regimens are nat equivolent with respect to the degree and duration af acid suppression ar suppressian of nacturnol acid.
The superiority of ranitidine aver cimetidine in these triols indicates that the dasing regimen currently recommended for cimetidine is less likely ta be as successful in maintenance therapy.

Zantac® 150 h.s.
ranitidine HCl/Glaxo 150 mg tablets

Glaxo / ROCHE®

See next page far references and Brief Summary af Product Informatian.

ZAN375 July 1987

References: 1. Silvis SE, Griffin J, Hordin R, et al: Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487.
2. Gough KR, Korman MG, Bardhan KD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse: A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984;ii:659-662.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathalagical hypersecretory conditians** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesaphageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Although recommended doses of ZANTAC do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Lack of experience to date precludes recommending ZANTAC for use in children or pregnant patients. Since ZANTAC is secreted in human milk, caution should be exercised when administered to a nursing mother.

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to ZANTAC® administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

There have been rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duadenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretary Conditians (such as Zollinger-Ellison Syndrame): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) In a dry place. Protect from light. Replace cap securely after each opening.

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2121 056

Glaxo
Glaxo Inc.
Research Triangle Park, NC 27709

(Continued from Page 379)

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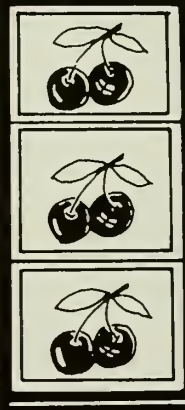

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BUY AN ARIZONA PRACTICE. We're the medical practice specialist of Arizona. FREE registration. Contact T. Ross, MD, Realty Executives, 6520 N. Scottsdale Rd, M-110, Scottsdale, AZ 85253; (602) 991-4273.

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(Continued on Page 383)

(Continued from Page 382)

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 1988, Fairbanks.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 9-12, 1987, Beaver Run, Breckenridge.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1988, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1987, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1988, Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 9-11, 1987, Marriott Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 17-20, 1987, Sheraton, Tacoma.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

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Before prescribing, please consult complete product information, a summary of which follows:

MICROBIOLOGY The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

GRAM-NEGATIVE AEROBES Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neissena gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neissena meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, e g , penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

GRAM-POSITIVE AEROBES Staphylococcus aureus (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

GRAM-NEGATIVE AEROBES Citrobacter freundii, Citrobacter diversus, Providencia species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*.

ANAEROBES Bacteroides species, *Clostridium* species (Note most strains of *C difficile* are resistant)

SUSCEPTIBILITY TESTING Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45 493-496, 1966, Standardized Disk Susceptibility Test, *Federal Register* 39 19182 19184, 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

DILUTION TECHNIQUES Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained

E coli ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neissena gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*.

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

PROPHYLAXIS The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

ROCEPHIN® (ceftriaxone sodium/Roche)

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS —pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after IV administration

HYPERSENSITIVITY —rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC —eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL —diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC —elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL —elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM —headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY —moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS —diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis

DOSAGE AND ADMINISTRATION Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g , dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1962 01)
Vials containing 500 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1963 01)
Vials containing 1 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1964 01)
Piggyback bottles containing 1 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1964 03)
Vials containing 2 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1965 01)
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* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

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Please see adjacent page for summary of product information.